Malaysian J Pathol 1993; 15(1): 35 – 39

Critical care aspects of dengue haemorrhagic fever/dengue shock syndrome

BH YONG

Intensive Care Unit, Department of Anaesthesiology, Faculty of Medicine, University of Malaya, Kuala Lumpur.

INTRODUCTION

Between January 1990 and September 1992, thirty patients ranging in age from 7 months to 43 years with a diagnosis of dengue fever (DF) or dengue haemorrhagic fever (DHF) were admitted to the Intensive Care Unit (ICU) of the University Hospital, Kuala Lumpur. 21 of these patients were serologically confirmed to have dengue infection by either IgM-capture ELISA and/or haemagglutination inhibition (HI) tests. 8 seropositive patients died. Death resulted from a number of inter-related causes - hypovolaemic shock, disseminated intravascular coagulation (DIVC), intracranial haemorrhage, hepatic encephalopathy, secondary bacterial sepsis and multi-organ failure. It is significant that 6 of the 8 deaths occurred in patients 19 years or older, and shows that serious illness from dengue is not confined to the paediatric age group.

PATHOPHYSIOLOGY

An appreciation of pathophysiological mechanisms is relevant to the management of critically ill dengue patients. Cytokine mediated mechanisms[1,2,3] cause an acute increase in vascular permeability which may lead to shock, acute renal failure and a tendency to develop pulmonary oedema. Coagulopathies result from both qualitative and quantitative platelet defects: decrease in clotting factors' especially Factor 8, prothrombin and fibrinogen, and activation of the fibrinolytic system. There is also evidence of increased capillary fragility. Further, there are as yet poorly understood direct viral effects on the liver, and possibly the brain and other organs.

PRINCIPLES OF MANAGEMENT

The principles of management hinge on (i) careful clinical assessment and a level of monitoring which is both appropriate to the level of physiological derangement as well as anticipatory of rapid changes, (ii) appropriate and early volume resuscitation and correction of coagulopathies, and (iii) prevention and treatment of complications including organ system support if neccessary.

The 1986 WHO Hospital Flow chart[5] for the management of dengue patients details appropriate monitoring and intervention, depending on physiological status. Monitoring centres on observation of the clinical signs of perfusion, blood pressure, pulse rate and pressure, urine output, and determination of haematocrit (PCV), platelets, serum electrolytes and blood gases. Treatment is based on fluid resuscitation with crystalloid or colloid, correction of electrolyte and acid-base imbalance, avoiding fluid overload and correction of coagulopathies. We have observed a subset of patients who fall outside the guidelines of the 1986 WHO chart. Such patients have a PCV which is not rising, are not fluid overloaded and have no overt evidence of haemorrhage but continue to deteriorate. These patients may require more intensive monitoring of their fluid status to determine appropriate fluid therapy, exclusion of CNS pathology (such as cerebral oedema or haemorrhage), and a search for bacterial sepsis. If deterioration continues, organ system support including ventilation, inotropes and dialysis may be necessary.

CRITERIA FOR REFERRAL

The key to management and prevention of complications is early intervention. The following criteria are offered as guidelines for referral or transfer of the patient to an area where a closer level of monitoring and care is available, such as an acute care ward, high dependency ward, or intensive care unit. Obviously this will need to be modified according to local availability of expertise, equipment and facilities for transport of critically ill patients. Many patients can be managed at peripheral centres provided there is adequate monitoring and trained personnel are available. The criteria are by no means exhaustive but cover the most commonly affected systems.

Address for correspondence and reprint requests: Dr. BH Yong, Intensive Care Unit, Department of Anaesthesiology, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur, Malaysia.

A) Cardiovascular impairment

Evidence of severe intravascular depletion and poor tissue perfusion not responsive to initial fluid therapy:

hypotension with systolic BP <100mmHg, pulse pressure <20 mmHg or postural hypotension. These signs may occur late and indicate serious derangement.
mottled cold peripheries with poor capillary refill.
mental confusion.
oliguria <0.5 ml/kg/hr.
metabolic acidosis.

B) Respiratory impairment

- persistent tachypnoea >40/min in adults.
- exhaustion: PaO_2 may be normal with supplementary O_2 but metabolic acidosis is usually present with a compensatory decrease in $PaCO_2$.
- hypoxia: clinical cyanosis; SaO <94% or PaO_2<80 mmHg on O_2 or a PaO_2/FiO_2 ratio <220. These margins are generous because of the serious sequelae of a hypoxic event.
- clinical evidence of pulmonary oedema or large pleural effusions.
- chest X-ray (CXR) showing increasing pulmonary infiltrates (2 quadrants or more).

C) Neurological impairment

- deterioration in mental status e.g. using the Glasgow Coma Scale. Some patients may remain conscious till the preterminal stage while others present with encephalopathy early.
- poor cough or gag reflex on pharyngeal suction.
- clinical evidence of raised intracranial pressure (late sign).
- CT scan evidence of cerebral oedema or haemorrhage.

D) Coagulopathy

- clinical evidence of abnormal bleeding e.g. from gastrointestinal tract or venepuncture sites.
- platelet count of <20,000/μL. It is known that a rapid drop in platelets correlates with extensive plasma leakage and may herald impending circulatory failure.[6] Volume replenishment e.g. with fresh frozen plasma is required. In the presence of bleeding at a platelet count of <50,000/μL, transfusion with platelet concentrate has been recommended.

CASE REPORTS

Over the last decade various unusual modes of presentation have been noted in severe dengue infection: particularly in adults. The following case reports illustrate the wide spectrum of these unusual clinical manifestations.

Case 1

A 43-yr-old female presented on day 5 of fever with chills, rigors, headache, vomiting and diarrhoea. There was no rash or petechiae. Examination revealed normal sensorium, BP 130/80 mmHg, pulse 84/min, temperature 38.2°C with mild dehydration. The chest was clear and the liver was enlarged to 2 cm below the costal margin. PCV was 37, platelets 43,000/μL. The WHO class was DHF Grade 1. Within 24 hr there was giddiness, blood stained vomitus, tachycardia, hypotension with BP 70/40 mmHg, and anuria. Prothrombin ratio was 2.24 and there was metabolic acidosis. CXR showed pulmonary congestion. With fluid therapy, BP was restored initially but she subsequently went into shock again and suffered a cardiac arrest. She was resuscitated but had generalised oozing with cold peripheries. CT scan showed mild cerebral oedema but no haemorrhage. DIVC indices were positive. She died 4 days after admission. The diagnosis was dengue shock syndrome with multiorgan failure. Serology: HI and IgM positive.

Comment: The salient features are an early onset of shock and DIVC. Dengue shock syndrome most commonly occurs from day 3 to 7 of the febrile illness.

Case 2

A 24-yr-old female presented on day 3 of fever with vomiting, headache, chills and rigors. There was no diarrhoea, petechiae or bleeding. Examination showed normal BP and pulse. Temperature was 38°C. The chest was clear. Hb was 14g/dl and platelets was 60,000/μL. The WHO class was DHF Grade 1. On the same day, she became hypotensive with systolic BP 80 mmHg, temperature 40°C. She had blood stained sputum, abdominal pain and distension. Clinically, she was hypovolaemic and had developed a right pleural effusion, crepitations and ascites. Petechiae were evident. Platelets were 11, 000/μL; blood gases showed hypoxaemia and CXR

showed extensive pulmonary infiltrates. Fresh frozen plasma, platelets and antibiotics were given. On day 4 she developed respiratory distress and suffered a hypoxic cardiac arrest. She was successfully resuscitated. CXR showed pulmonary oedema. The CVP was 10 mmHg. The liver transaminases rose to >500 IU/L and she developed marked liver and renal impairment, but did not require dialysis. Secondary bacterial sepsis supervened, with line-related *Streptococcus faecalis* and isolation of *Pseudomonas* and *Acinetobacter* spp. from the respiratory tract. Because of prolonged respiratory support she required a tracheostomy, which was complicated by malposition leading to bilateral pneumothoraces and pneumomediastinum. After a prolonged 6 week stay in ICU she recovered with liver enzymes and serum creatinine back to normal limits, was weaned off the tracheostomy and discharged. Serology: HI and IgM positive.

Comment: Early onset of shock is again seen. In addition, respiratory pathology was prominent and it was difficult to decide between pulmonary oedema, haemorrhage and infection as the cause of the extensive infiltration seen on CXR. The clinical picture falls within the extended definition of Adult Respiratory Distress Syndrome (ARDS).[8,9] Hepatic and renal involvement were also features of the illness.

Case 3

A 19-yr-old female presented on day 4 of fever with chills, headache and vomiting. BP was 110/80 mmHg, pulse 86/min, temperature 37.5°C. The chest was clear. Hb was 12.7 g/dl, platelets 62,000/μL. The WHO class was DHF Grade 1. Three days later she developed generalised fits, became jaundiced and had oozing from venepuncture sites. CT of the brain showed cerebral oedema. Liver transaminases and serum creatinine were raised. DIVC indices were positive. The platelet count dropped to 16,000/μL. She was not hypotensive but had a low urine Na+. CXR showed clear lung fields. Subsequently, she developed gastrointestinal bleeding, oliguria, metabolic acidosis and was ventilated. EEG showed diffuse severe abnormalities consistent with encephalopathy. There was persistent liver and renal failure which was treated with continuous veno-venous haemofiltration/dialysis. She developed bacterial sepsis, was severely hypercatabolic and died 4 weeks after admission. The diagnosis was DHF with secondary bacterial sepsis and multiorgan failure. Serology: IgM positive.

Comment: Liver impairment occurred very early in the illness, with hepatic encephalopathy and cerebral oedema. In addition, renal failure was severe and was a major contributory factor to the patient's eventual demise. In contrast to case 2, there were few respiratory signs.

Case 4

A 26-yr-old male presented on day 3 of fever with backache, retrobulbar pain, chills and nausea. There was no rash, BP and pulse were normal and chest examination revealed crepitations. PCV was 49 and platelets 57,0001 μL. The WHO class was DHF Grade 1. The following day he developed tachypnoea. PCV was 51 and platelets 25, 000/μL. CXR showed pleural effusion with pulmonary infiltration which progressively worsened. Serum creatinine was 160 umol/L. He had a transient hypotensive episode with BP 90 mmHg and developed hypoxaemia with PaO_2 50 mmHg on O_2 10L/min by mask. The clinical and radiological picture was consistent with ARDS. He was ventilated for 3 days and recovered with no disability. Serology: HI and IgM positive.

Comment: This case illustrates primary respiratory involvement with very little other organ involvement apart from a transient rise in serum creatinine.

It should be remembered that the majority of dengue patients have a mild illness and recover. The cases presented and the discussion that follows refer to a highly selected group of severely ill cases who were managed in the intensive care unit. The multiorgan involvement of severe dengue infection present many challenging problems in management. The following clinical scenarios detail some of the problems we have encountered, and suggested therapeutic strategies are discussed.

PROBLEMS IN MANAGEMENT

1. What are the indications for ventilation?

This will obviously depend on available facilities, expertise and monitoring. Classical criteria of respiratory failure are when PaO_2 is <50 mmHg or O_2 saturation is <90%. However, some patients demonstrate severe metabolic acidosis, tachypnoea and exhaustion at an early stage and respiratory support should be considered before hypoxia supervenes. Another group of patients will be those with decreased consciousness who are unable to protect their airway. Ventilation

may also be neccessary for intracranial pressure (ICP) control.

2. *What are the guidelines for fluid therapy in patients with pre-renal failure with 'leuky' lung capillaries?*

Serial measurements of PCV provide the most useful guide to fluid therapy in patients without bleeding or DIVC. A urine output of at least 0.5 to 1 ml/kg/hr should be maintained. Careful titration of fluids is neccessary to avoid pulmonary oedema. In the oliguric patient, we have found urine Na+ concentration useful, with < 20 mmol/L indicating volume depletion and need for further fluids.[10] (Rarely, in hepatorenal syndrome, a low urinary Na+ not responsive to fluids may be seen.) A central venous line (CVL) is often inserted to guide fluid therapy, but some pitfalls must be avoided. Single readings may be misleading especially in severely tachypnoeic patients. If the CVL is connected to a pressure transducer it will be seen that large negative swings on inspiration can markedly affect the mean reading given by a water manometer. It is much more instructive to use the trend and to assess the response to a fluid challenge. In adults we use aliquots of 100-200ml. The use of a pulmonary artery catheter must be weighed carefully, particularly in patients with severe coagulopathy. ARDS and septic shock with oliguria are situations where its use may be justified.

3. *Management of hepatic encephalopathy in dengue*

Decreased consciousness may result from cerebral oedema, hepatic encephalopathy, hypoxia, intracranial haemorrhage or decreased cerebral perfusion in dengue shock syndrome. Cerebral oedema is probably vasogenic in origin secondary to increased capillary permeability. Whether the dengue virus has any direct cytotoxic effect on the brain has not been shown. In contrast to hepatic encephalopathy from other causes where moderate fluid restriction may be desirable, overzealous restriction of fluid in the acute stage of dengue may lead to renal failure and decreased perfusion to tissues including the brain. Meticulous fluid balance as outlined above will need to be maintained. Measures to control ICP include ventilation to regulate $PaCO_2$ without causing excessively high intrathoracic pressure, a head-up tilt, and avoidance of neck compression. Frusemide is useful as it reduces CSF production and potentiates the effect of mannitol.[11] Mannitol (at a dose of 0.5-1 g/kg) should be used with great caution in view of increased capillary permeability both in the lungs and the brain. Breakdown of the blood-brain barrier in dengue infection leading to cerebral oedema has been shown in animal studies.[12] In established renal failure mannitol should be used only in conjunction with dialysis. The role of ICP monitoring in dengue remains to be clarified. We have used a subdural catheter in one patient, where the option to withdraw CSF has been of benefit in ICP control. Balanced against this is the risk of haemorrhage. Other ancillary measures in patients with hepatic encephalopathy are anticonvulsants and lactulose[13] at a dose sufficient to produce diarrhoea 2-3 times daily to reduce absorption of nitrogenous compounds.

4. *Secondary bacterial sepsis*

It is not surprising that the clinical picture seen in severe dengue infection is very similar to that in septic shock, as cytokines[2,3,14] are implicated in the pathophysiology of both conditions. Critically ill patients have multiple portals of entry for secondarily infecting organisms e.g. endotracheal tubes, urine catheters and monitoring lines. The dengue virus has also been shown to transiently suppress immune function in animal studies.[15] Whether dengue virus infection facilitates secondary bacterial sepsis has not been investigated. It is often difficult to decide when bacterial sepsis has supervened in a patient with dengue. Many patients will fulfil the consensus criteria for definition of the sepsis syndrome[16] i.e. clinical evidence of infection like tachypnoea, tachycardia, hyper- or hypothermia in association with evidence of altered organ perfusion. It is our practice to start antibiotics in all critically ill dengue patients in the intensive care unit. In septic shock infecting organisms have been shown to originate endogenously from the gut due to gut ischaemia.[17] Selective decontamination of the gastrointestinal tract with non-absorbable antibiotics have been investigated in an attempt to reduce nosocomial infection.[18,19] However, no clear improvement in survival has been shown and selective decontamination is not used in our unit. Enteral feeding is important in maintaining gut integrity and it is our practice to start feeding enteral electrolyte solutions at an early stage, followed by an enteral nutritional formula. Finally, the role of strict aseptic practice, particularly handwashing, in reducing secondary infection cannot be overemphasised.

CONCLUSION

Infection with the dengue virus may present with varied clinical manifestations. The disease may be potentially fatal in a small number of patients. Many of the complications leading to death are potentially treatable and reversible. With appropriate monitoring and aggressive intervention at an early stage, many of these patients may be saved.

REFERENCES

1. Funahara Y, Sumarmo, Shirahata A, Setiabudy-Dharma R. DHF characterised by acute type DIC with increased vascular permeability. Southeast Asian J Trop Med Pub Hlth 1987; 18: 346-50.
2. Khanna M, Chaturvedi UC, Sharma MC, Pandey VC, Mathur A. Increased capillary permeability mediated by a dengue virus- induced lymphokine. Immunology 1990; 69: 449-53.
3. Kurane I, Ennis FE. Immunity and immunopathology in dengue virus infections. Semin Immunol 1992; 4: 121-7.
4. Halstead SB. Dengue: Hematologic aspects. Semin Hematol 1982; 19: 116-31.
5. WHO. Dengue Haemorrhagic Fever: Diagnosis, Treatment and Control. Geneva, WHO, 1986: 50-1.
6. Rohde JE. Clinical management of severe dengue. Trop Doctor 1978; 8: 54-61.
7. George R, Liam CK, Chua CT, *et al*. Unusual clinical manifestations of dengue virus infection. Southeast Asian J Trop Med Pub Hlth 1988; 19: 585-90.
8. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the Adult Respiratory Distress Syndrome. Am Rev Resp Dis 1988; 138: 720-3.
9. Matthay MA. The Adult Respiratory Distress Syndrome - new insights into diagnosis, pathophysiology and treatment. West J Med 1989; 150: 187-94.
10. Fisher MM. Acute Renal Failure. In: Oh TE, ed: Intensive Care Manual. Sydney: Butterworths, 1990: 246-51.
11. Messick JM, Newberg LA, Nugent M, Faust RJ. Principles of Neuroanaesthesia for the non-neurosurgical patient with CNS pathophysiology. Anesth Analg 1985; 64: 143-74.
12. Chaturvedi UC, Dhawan R, Khanna M, Mathur A. Breakdown of the blood-brain barrier during dengue virus infection of mice. J Gen Virology 1991; 72: 859-66.
13. Mullen KD, Weber FL. Role of nutrition in hepatic encephalopathy. Semin Liver Dis 1991; 11: 292-302.
14. Bone RC. The pathogenesis of sepsis. Ann Intern Med 1991; 115: 457-69.
15. Pang T. Pathogenesis of dengue haemorrhagic fever: towards a more balanced view. Southeast Asian J Trop Med Pub Hlth 1987; 18: 321-5.
16. The ACCP/SCCM Consensus Conference Committee. Definitions of sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101: 1644-55.
17. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the develspment of systemic infection and multiorgan failure. Arch Surg 1990; 125: 403-4.
18. Gastinne H, Wolff M, Delatour F, Faurisson F, Chevret S. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. N Engl J Med 1992; 326: 594-9.
19. Hartenauer U, Thulig B, Diemer W, *et al*. Effect of selective flora suppression on colonization, infection and mortality in critically ill patients: a one year, prospective consecutive study. Crit Care Med 1991; 19: 463-73.