Original Article

Clinical Features, Complications and Atypical Manifestations of Children with Severe forms of Dengue Hemorrhagic Fever In South India

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ABSTRACT

Objective. To review clinical features and outcome of children with severe forms of dengue hemorrhagic fever (DHF) presenting to a pediatric intensive care unit (PICU) with particular focus on clinical presentation and outcome.

Methods. Retrospective chart review of patients admitted to the Pediatric Intensive Care Unit (PICU) of a referral children's hospital in South India with DHF over 1.5 years (2001-January 2003).

Results. Of 858 patients with dengue fever/DHF admitted to the hospital during the study period, 109 cases with severe forms of disease required PICU admission, of which 9 patients died. 77 were under 5 years of age. The commonest indication for PICU admission was persistent shock (39 patients) followed by requirement for positive pressure ventilation in 29 patients (10 of whom had Acute Respiratory Distress Syndrome [ARDS]) and neurological symptoms in 24 patients. An important finding was the presence of diastolic dysfunction in 3 children. Six deaths of refractory shock included 4 who had ARDS and DIC and 2 who had shock with DIC 3 patients had abdominal compartment syndrome (ACS) has not been previously described in children with DSS and may lead to fluid refractory shock if not corrected. All patients had thrombocytopenia which was a defining feature of the syndrome, while 74 were also coagulopathic and 6 had severe fatal DIC. Hepatic dysfunction was more severe in children with prolonged shock, however, only a fifth of cases (5/24) with neurological manifestations were in shock. Other significant reasons for neurological presentation included cerebral edema, and encephalopathy secondary to hepatic dysfunction. 2 children had features of Acute Disseminated Encephalomyelitis (ADEM), previously only described in adults with dengue.

Conclusion. It was found that complications such as DIC, diastolic dysfunction, abdominal compartment syndrome, ARDS and hepatic dysfunction were more frequent in severe established shock. However, most neurological events were unrelated to the perfusion status. Children referred late were harder to resuscitate. There were 9 PICU deaths (case fatality rate of 8.35%). Severe refractory shock, DIC, ARDS, hepatic failure and neurological manifestations singly or in combination were the commonest causes of death in the present study. **[Indian J Pediatr 2006; 73 (10) : 889-895]**

Key words : *Dengue hemorrhangic fever; Dengue shock syndrome; Acute respiratory distress syndrome; Compartment syndrome; Diastolic dysfunction.*

Dengue, the most important mosquito-borne viral disease affecting humans, occurs in over 100 countries and threatens the health of more than 2.5 billion people of the tropics and subtropics.[1-4] Dengue viral infections, caused by any of the four dengue serotypes (DEN 1-4), are amongst the leading causes of hospitalization and death amongst children in several tropical countries.[1] The case-fatality rate of dengue hemorrhagic fever (DHF) in most countries is about 5%; most fatal cases are among children.[1-4]

The majority of hospitalized children with dengue fever, DHF/DSS recover uneventfully with meticulous supportive treatment; however, a small percentage of critically unstable patients require pediatric intensive care unit (PICU) admission and can have significant mortality. These are a unique group that may have protean manifestations, both severe forms of the expected manifestations (shock and bleeding) and atypical manifestations, singly or in combination. There is limited literature describing DHF in children admitted to an intensive care unit.

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The aim of the present study was to review previously described as well as atypical clinical features and outcome of critically unwell children with severe DHF and dengue shock syndrome (DSS) presenting to PICU.

MATERIAL AND METHODS

The authors examined the records of 109 consecutive patients with complicated and serious forms of DHF Grades III and IV (DSS) admitted to the PICU of the Kanchi Kamakoti CHILDS Trust Hospital, Chennai, over a 1.5-year period beginning June 2001. The charts were obtained from the medical records department and data was entered on a spread sheet by one of the authors (SRK) and crosschecked for accuracy and completeness by SR.

Case Definition : During a prevailing epidemic, the clinical diagnosis of DHF is based on four major characteristic manifestations[1,2] a history of fever lasting for 2-7 days, hemorrhagic manifestations (petechiae, palatal or gum bleeds, hematemesis or malaena), thrombocytopenia (platelet count ≤100,000 cumm), evidence of plasma leakage manifested by hemoconcentration (an increase in the hematocrit 20%) or pleural effusion or ascitis.[1,2] In children with DSS, the plasma leakage is extensive enough to result in shock. The diagnosis of dengue fever in the present study institution was based on clinical findings[1], but was confirmed by serology employing IgM and IgG-capture enzyme linked immunosorbent assay (MAC-ELISA). This test is based on finding dengue-specific IgG and IgM antibodies in the patient's serum.[1,2] In the patients in whom the assays were not performed, alternative serologic tests were done to establish either a high acute phase dengue specific antibody titre or a 4-fold or greater rise in antibody titres between the acute and convalescent phase serum samples.[1,2] Patients in whom the serological tests were negative (or the rising convalescent titre could not be collected) but with characteristic features of DHF or DSS were included if no alternative bacterial or viral cause for the illness was identified.

The case fatality rate (CFR) was that of patients with DHF and DSS who died from complications of their disease during their hospital stay.

Disease severity was assessed according to the WHO grading system[1]

Grade I - Positive tourniquet test
Grade II - Spontaneous bleeding
Grade III - Circulatory failure
Grade IV- Undetectable blood pressure and pulse

Grades III and IV DHF are also referred to as Dengue Shock Syndrome (DSS)

Indications for ICU admission : All children with DHF were triaged in the Emergency Room. PICU admission was standardized for severe cases of DHF in the event of:

- DHF Grade III or IV(DSS) with shock unresponsive to 30-40 ml/kg fluids (Isotonic crystalloids ± colloids).
- Severe bleeding manifestations.
- Complicated course *i.e.*, involvement of respiratory/ neurological/hepatic/renal systems.
- Need for assisted ventilation
- Moribund state

Cases with DF and DHF that did not qualify for PICU admission were admitted to the High-Dependency and step down wards. Some admissions to the PICU included those patients who were transferred from other wards in the hospital when their clinical status worsened due to progression of shock or occurrence of complications.

MANAGEMENT

All children were managed with fluids and blood products according to standard WHO guidelines.[1,2]

RESULTS

Of the 858 hospital admissions with dengue fever during the study period, 109 cases (12.7%) were admitted to the PICU. Of these, 55 were males. Children less than 5 years were most commonly afflicted with severe disease (77 patients, 70% of all cases) with infants forming the largest sub-group.

Primary and Secondary Infections

Fifty-one children (46.7%) had primary dengue infection and 45 (41.2%) had secondary dengue infection. The serology was negative in 13 patients, however, no alternative cause for the illness was identified.

Clinical Presentation to the PICU

Grade at presentation: Two thirds of all children (73 patients) were in DSS of which 27 presented in DHF grade IV. The remaining 36 patients comprised those in Grade I & II DHF who presented with complications (neurologic /respiratory/ hepatic) or those that progressed to DSS during hospitalization.

Table 1. Cardiovascular Manifestations in Severe Forms of DHF

Cardiovascular disorder (percentage)	Number (Percentage)	Deaths
• Persistent shock	39 (37.5%)	6#
• SVT	1 (0.9%)	-
• Myocardial dysfunction (Echocardiographic)	5 (4.6%)	
o Systolic dysfunction	2 (1.8%)	
o Diastolic dysfunction	3 (2.7%)	
Pericardial effusion	3 (2.7%)	-
Cardiac arrest (in Emergency Room)	2 (1.8%)	1*

4 patients had shock with ARDS and DIC, 2 had persistent shock. with DIC; *Death in Emergency Room was not included in PICU CFR

Hemodynamic and Cardiovascular Manifestations

The commonest cardiovascular complication encountered was persistent shock despite fluid administration in the Emergency Room in accordance with the WHO regimen (Table 1).

Thirty-nine children (37.5%) remained in shock despite administration of at least 40 ml/Kg of fluids and blood products (whole blood, packed red blood cells ± fresh frozen plasma as indicated). These patients were initiated on inotropes and/or vasopressors and their myocardial function and filling status were assessed by echocardiography.

Serial echocardiographic evaluation by a pediatric cardiologist was carried out in 43 children, 3 of whom had diastolic dysfunction necessitating therapy with a lusitropic agent such as milrinone. Systolic dysfunction was documented in 2 patients. 3 children had small pericardial effusions. Repeat echocardiographic evaluation at discharge from the PICU was normal in all survivors.

Thirty-two of the 39 patients with persistent shock improved with ongoing supportive treatment (further fluids, blood products, vasoactive agents and, where indicated, positive pressure ventilation).

The cause of fluid refractory shock in one patient was unstable supraventricular tachycardia (SVT) which reverted with adenosine and the patients circulatory status normalized. Two children referred to the hospital in pulseless DHF Grade IV shock suffered a cardiopulmonary arrest in the Emergency Room, one was successfully resuscitated and transferred to the PICU and recovered with ongoing supportive treatment. Six children died of refractory shock . This was complicated by Acute Respiratory Distress Syndrome (ARDS)[5] and disseminated intravascular coagulation (DIC) in 4 patients; 2 had DIC in addition to refractory shock.

Abnormal Fluid Collection

Apart from shock, third spacing was manifest as pleural effusion in 55 children (50.4%). 51(46.7%) had ascitis, 8 children had profound generalized anasarca and 3 children had pericardial fluid accumulation as described above.

Compartment Syndrome

Of the 27 children with DHF Grade IV, compartment syndrome was seen in 3 children and contributed to refractory shock.[6] The intra-abdominal pressure was estimated by measuring the bladder pressure *via* an indwelling Foley catheter. Improvement in cardio-respiratory function occurred in 2 children following controlled release of the intra-abdominal pressure by peritoneal dialysis while the third failed to improve and expired.

Hematological features

Although all patients had platelet counts < 100,000/cumm (part of case definition of DHF), 69 patients (63%) had evidence of hemorrhagic manifestations such as spontaneous skin and mucus membrane bleeds, upper or lower gastro-intestinal tract (GIT) bleeds and prolonged ooze from venepuncture sites. Severe hemorrhagic manifestations contributing to shock due to spontaneous GIT hemorrhage was seen in 18 patients (16.5%). Of these, 2 patients remained in shock with DIC and massive fatal bleeding despite maximal supportive treatment and could not be resuscitated.

The mean hematocrit at presentation was 35.5 ± 8.1% . The mean platelet count was 54,443 ± 39,623/cumm. Twenty children had platelet counts below 20,000/cumm.

Disordered coagulation (prolongation of the prothrombin and/or partial thromboplastin time) was seen in 74 children (67.8%). 16 children had disseminated intravascular coagulation (DIC) of which 6, that also had refractory shock, died.

Respiratory manifestations

In addition to pleural effusions in 55 patients, 10 children satisfied the criteria for ARDS, all of whom presented with Grade IV DHF and there were 4 deaths in this group. 29 children (26.6%) were ventilated, the indications being ARDS in 10 patients, neurological indications in 9, decompensated shock in 9 and following cardiac arrest in one. Mean duration of ventilation was 4.3 ± 2.8 days.

Neurological Manifestations

Twenty-four children had neurological manifestations (Table 2) of which only 5 were in shock. Seventeen patients with suspected dengue encephalopathy presented with altered mental status and seizures. Following improvement of the cardio-respiratory status, all patient that remained in altered mental status underwent imaging with computerized tomographic (CT) scans and cerebrospinal fluid (CSF) analysis. The CSF was abnormal in three patients, 2 of whom had raised protein and lymphocytic pleocytosis. One child with Grade II DHF had CSF features of acute bacterial meningitis which was confirmed on culture. Dengue antibodies were not detected in the CSF in any child and

Table 2. Neurological Manifestations (Total- 24)

Neurological manifestations	Number of cases	Number of Deaths
Dengue encephalopathy	17	-
Bacterial meningitis	1	-
Acute Disseminated Encephalomyelitis (ADEM)	2	1
Hepatic encephalopathy	2	1
Sub-arachnoid hemorrhage	1	1
Cardiac arrest sequelle	1	-

the CT scans were unremarkable apart from a sub-arachnoid bleed in one patient and moderate cerebral edema in 8 children.

Two children continued to have profound altered mental status and no localizing signs despite normalization of their cardiopulmonary and metabolic parameters and subsidence of stigmata of DHF (*i.e.*, normalization of platelet counts, resolution of pleural effusions and stable hematocrit). Magnetic Resonance Imaging (MRI) of the brain with diffusion weighted imaging (carried out on week 2 of PICU stay) revealed hyperintense lesions suggestive of Acute Disseminated Encephalomyelitis (ADEM).[7,8] Both patients received pulse steroids. One patient progressed to severe cerebral edema and brain stem death, the second survived with significant neurological residua.

Other neurological manifestations included 2 children with DHF Grade IV and hepatic encephalopathy (one death) and one with an extensive sub-arachnoid hemorrhage that expired. One patient resuscitated from cardiac arrest had hypertonia and convergent squint but improving mental status. Of the 21 survivors with neurological manifestations, 19 experienced a complete recovery.

Renal issues

Acute renal failure was encountered in 5 children presenting with oligo-anuria and a mean creatinine value of 2.2 ± 0.6 mg/dl, all of whom underwent peritoneal dialysis and improved. Peritoneal dialysis was also initiated in 6 additional children with diuretic resistant fluid overload and severe respiratory distress. Three of these children had compartment syndrome and one patient died as described above.

Hepatic dysfunction

Hepatic dysfunction was seen in 40 children (36.6%), all of whom had greater than a three-fold elevation of hepatic transaminases. 32 of 40 children with liver dysfunction had presented in DSS (Grade III or IV DHF). The highest values of transaminases were 10,500 IU/L(ALT) and 3700 IU/L(AST) seen in one of two children who presented with fulminant hepatic failure and expired. Hepatic parameters of all other children were normal at the time of discharge from the ICU.

Co-infections

Co-infections were suspected in the presence of unusual clinical and/or laboratory features and were confirmed in 19 patients, all of whom also had positive dengue serology. 9 children had leptospirosis, 6 children had enteric fever, three had malaria and one had bacterial meningitis in addition to DHF. All co-infections responded to appropriate drug and supportive therapy in addition to fluid resuscitation.

Duration of PICU stay : The mean duration of PICU stay was 4.9 ± 2.9 days.

Case fatality rate (CFR) : Nine out of 109 cases with severe forms of DHF died resulting in an ICU CFR of 8.3%. The overall hospital CFR for all forms of dengue viral infections was 1.05%. A post-mortem examination was not performed in any patient.

Cause of death in 9 children : Refractory shock with DIC and ARDS – 4 (1 also had compartment syndrome)

Refractory shock with DIC - 2

Fulminant hepatic failure with encephalopathy – 1

Acute disseminated encephalomyelitis - 1

Sub-arachnoid hemorrhage –1

DISCUSSION

Here are reported complicated and atypical manifestations in the largest series focusing specifically on patients with severe forms of DHF requiring Pediatric Intensive Care. The commonest indication for PICU admission was persistent uncorrected shock followed by respiratory distress and neurological symptoms. Findings not previously described in the setting of DHF/DSS include abdominal compartment syndrome (ACS), diastolic dysfunction contributing to refractory shock and Acute Disseminated Encephalomyelitis (ADEM) worsening the neurological status.

Although there was no sex predilection, severe disease occurred most often in infants followed by the 1–5 year age group. While severe dengue infections have been reported in infants[9-11], the present study results were in contrast to a study from all hospitalized patients with dengue fever and DHF in the same institution where the commonest age group was 5-15 years.[12]

With respect to circulatory complications, 39 (37.7%) presented with shock refractory to Emergency Room fluid resuscitation An important cause of persistent shock in a patient with DSS whose circulatory status fails to improve despite adequate fluids is internal hemorrhage[1,2], hence all patients with fluid refractory shock received blood transfusion (packed red blood cells and plasma) unless hemoconcentration persisted or an obvious cause such as SVT was identified. Failure of the systemic perfusion to improve despite fluid and blood transfusion led to echocardiographic evaluation of the myocardial function: an unexpected finding was the presence of diastolic dysfunction[13] in 3 cases. This feature, although likely due to myocardial edema in the setting of gross anasarca has been previously reported by us in dengue [14] and has important implications for fluid resuscitation. Children with diastolic dysfunction are at a higher risk of elevated left ventricular filling pressures and resultant pulmonary edema with fluid challenges.[15] The finding may be missed unless Doppler studies are performed by an experienced echocardiographer and management includes small volume fluid resuscitation at slower rates, avoidance of tachycardia and use of non-catecholamine lusitropic agents such as the phospho-diesterase inhibitor

agent milrinone. Echocardiographic features of left ventricular dysfunction was obtained in only two patients. This was probably a gross under-estimation as all patients with fluid and blood product refractory shock were already on inotropes at the time of echocardiography, which may have "normalized" abnormal left ventricular systolic function.

A study of hemodynamic profiles in DHF from Thailand reported lowered cardiac index due to decreased ejection fraction and lowered preload[16] while reports from New Delhi, India have reported global hypokinesia[17,18] but there were no previous reports of diastolic dysfunction in DHF. Pericardial effusions have been reported previously, but did not contribute to the shock status.[19] Steroids were not used in cases of refractory shock as there was no data supporting it's use.[20] Unsurprisingly, all four patients with uncorrected shock and DIC expired.

The abdominal compartment syndrome (ACS) contributed to refractory shock in 3 children with DHF Grade IV that required large volume fluid resuscitation. ACS was defined as abdominal distention with intra-abdominal pressure (IAP) > 15 mm Hg, accompanied by at least two of the following: oliguria or anuria; respiratory decompensation; hypotension or shock; metabolic acidosis.[6] All of the above features may easily be thought to be part of the clinical spectrum of critically unstable DSS with refractory shock and fluid overload: the diagnosis of co-existing ACS may be missed unless specifically considered. Relief of the elevated intra-abdominal hypertension led to improved cardio-respiratory function in 2 children while the third died due to co-existing complications. ACS in the setting of DSS has not been previously described.

With respect to hematological complications, the mean hematocrit at presentation was 35.5 ±8.1%. Indian children with DHF have a lower than expected rise in hematocrit during the plasma leakage period: this has been attributed to the high prevalence of iron deficiency anemia in the general population.[21-23]

Platelet counts less than 50,000/cumm was noted in 62.3%. DHF patients with a platelet count < 50,000/cumm have been reported to have a six-fold higher mortality than those with platelet counts > 50,000/cumm[24] and in the present study too, only two of nine deaths occurred in children with platelet counts greater than 50,000/cumm. Immune related platelet damage and inhibition of platelet aggregation contribute to the thrombopathy.[25] Apart from decreased platelet number and function, DHF patients can have abnormal hemostasis (vasculopathy, coagulopathy and DIC).[26,27] DIC and massive fatal bleeding may be more frequent in children with prolonged shock.[27-29] In the present study, while frank DIC was seen in six cases, co-existing refractory shock resulted in death in 4 children.

Twenty-nine children (26.6%) required ventilation, the main indication being increasing respiratory distress. ARDS was seen in 10 children, 4 of whom died. All cases of ARDS occurred in children presenting with Grade IV shock and lung injury in these patients may have resulted from "shock lung" and/or increased capillary permeability.[30] The need for high airway pressures required to ventilate patients with severe ARDS in DSS can easily further worsen the patients' already precarious hemodynamics and it is not surprising that Dengue associated ARDS is associated with a high mortality.[31]

Hepatic and neurological dysfunction have been classified as "unusual complications/manifestations" of DHF.[32-34] Hepatic dysfunction may be multifactorial – the most important causes are prolonged shock, associated metabolic acidosis and DIC with resultant ischemic hepatitis.[32,33,35] The liver may also be the major site of dengue viral replication.[36-39]

Only one-fifth of the 24 children with neurological manifestations were in shock. While children with DSS may have abnormal neurology secondary to cerebral hypoperfusion on account of shock leading to hypoxic-ischemic events and/or intracranial bleeds,[32] other significant reasons for neurological presentations include cerebral edema, direct neurotropic effect of dengue virus resulting in encephalitis/encephalopathy, or secondary to hepatic dysfunction and metabolic derangements such as hypoglycemia and hyponatremia.[1,2,41-46]

Cranial imaging and CSF analysis were normal in the majority. 2 patients had clinical and MRI features suggestive of ADEM. While ADEM may occur following many viral exanthems[7,8] and Guillain Barre syndrome has been described in Indian children following dengue infection,[47] there has been only a single previous report on the occurrence of ADEM following dengue fever in an adult.[48]

The 3 neurological deaths in the present study were related to ADEM, sub-arachnoid hemorrhage and hepatic encephalopathy. In most cases, complete neurological recovery is the rule.[42,43] and in the present study too, neurological recovery was complete in 19 of 21 survivors.

Co-infections were seen in 17.4% and it is important that they be promptly recognized. Co-infections can modify the clinical presentation of dengue and result in missed or delayed diagnosis and treatment of dengue shock.[49]

The limitations of the present study relate to the inherent weakness of a retrospective analysis. The strengths relate to the fact that all cases were seen at a single centre by both the authors where the indications for admission to the PICU and subsequent management was standardized. Although a total of 858 cases were admitted to the entire hospital during the study period, 109 (12.7%) critically unstable cases of dengue fever were admitted to the PICU, making the present one the largest descriptive study of children specifically with severe forms of DHF requiring Intensive Care.

The clinical implications of our findings relate to the fact that critically unwell patients with dengue fever,

DHF and DSS may have complications singly or in combination related to virtually every major system. Early recognition in conjunction with meticulous monitoring and targeted supportive care is the cornerstone of a successful outcome. However, particularly in children that present late with refractory shock, it is important to be aware of entities such as diastolic dysfunction and ACS which, unless recognized and appropriately managed, may contribute a higher CFR.

If appropriately managed, the CFR for all hospitalized children with dengue fever may be as low as 0.2-5 % [1,2,35] with higher rates up to 12.6% in patients with DSS.[20] Mortality figures from Indian literature suggest CFR ranging from 26 to 47%.[50-52] A specific problem was late referrals in established shock and DIC. Children referred late are harder to resuscitate.[14,53] In our study, the ICU mortality was 8.3% while the overall hospital CFR for all forms DHF was 1.05%.

Severe refractory shock, DIC, ARDS, hepatic failure and neurological manifestations singly or in combination were the commonest causes of death in our series.

CONCLUSION

In conclusion, critically ill children with dengue may have protean manifestations. Most complications such as established and refractory shock, diastolic dysfunction, abdominal compartment syndrome, DIC, ARDS and hepatic dysfunction were more frequent in severe established shock. Neurological events, for the most part, were unrelated to the perfusion status .

Complications infrequently / not previously described in the setting of critically ill children with dengue viral infections include diastolic dysfunction, abdominal compartment syndrome and ADEM.

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