Review of Dengue Hemorrhagic Fever Fatal Cases Seen Among Adults: A Retrospective Study

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Abstract

Background: Dengue is a mosquito-borne viral disease endemic in many countries in the tropics and sub-tropics. The disease affects mainly children, but in recent years it is becoming more of an adult disease. Malaysia experienced a large dengue outbreak in 2006 to 2007, involving mostly adults, with a high number of deaths.

Methodology/Principal Findings: We undertook a retrospective study to examine dengue death cases in our hospital from June 2006 to October 2007 with a view to determine if there have been changes in the presentation of severe to fatal dengue. Nine of ten fatal cases involved adult females with a median age of 32 years. All had secondary dengue infection. The mean duration of illness prior to hospitalization was 4.7 days and deaths occurred at an average of 2.4 days post-admission. Gastrointestinal pain, vomiting, diarrhea, intravascular leakages and bleeding occurred in the majority of cases. DSS complicated with severe bleeding, multi-organ failure and coagulopathy were the primary causes of deaths. Seven patients presented with thrombocytopenia and hypoalbuminemia, five of which had hemoconcentration and increased ALT and AST indicative of liver damage. Co-morbidities particularly diabetes mellitus was common in our cohort. Prominent unusual presentations included acute renal failure, acute respiratory distress syndrome, myocarditis with pericarditis, and hemorrhages over the brain and heart.

Conclusions: In our cohort, dengue fatalities are seen primarily in adult females with secondary dengue infection. The majority of the patients presented with common clinical and laboratory warning signs of severe dengue. Underlying co-morbidities may contribute to the rapid clinical deterioration in severe dengue. The uncommon presentations of dengue are likely a reflection of the changing demographics where adults are now more likely to contract dengue in dengue endemic regions.

Introduction

Dengue virus (DENV) infection is a global health threat affecting at least 3.6 billion people living in more than 125 countries in the tropics and sub-tropics [1]. It is among the most important arthropod-borne diseases. All four dengue virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) can cause dengue. The disease can present as a mild self-limiting illness, dengue fever (DF), or as the more severe forms of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [2]. The World Health Organization (WHO) 2009 guidelines classify patients into three groups; dengue without warning signs, dengue with warning signs and severe dengue [3]. Clinical manifestation of severe dengue includes severe bleeding, severe organ involvement and severe plasma leakage. Most dengue deaths are associated with DHF/DSS (WHO 1997 guidelines) and severe dengue (WHO 2009 guidelines).

DF and DHF were first documented in Malaysia in 1902 and 1962, respectively [4,5]. A major dengue epidemic was recorded in 1973, and since then dengue has become endemic in Malaysia with major outbreaks occurring every 3–4 years [6,7]. There were a number of reports describing the clinical features and risk factors associated with the severe manifestations of dengue and dengue-related deaths during the first two decades following the 1973 epidemic. During this period, children were the most predominant group affected, hence contributed substantially to the clinical description of severe dengue [8,9,10]. In the last two decades, however, the number of dengue cases had escalated exponentially. There were 48,846 cases and 98 deaths in 2007 in Malaysia with those aged 15–35 years old contributing to at least 48% of the total number of dengue cases [11]. The trend of higher percentage of adults contracting dengue has also been reported in other dengue endemic countries [12]. This review of fatal cases of dengue infection was undertaken in light of this changing epidemiology of dengue in Malaysia and in this region.
Amplification was performed as previously described [14,15].

**Results**

**Virus Isolation and Genotyping**

Serology

The acute-phase serum samples were obtained from the UMMC Diagnostic Virology Laboratory Repository. Convalescent serum sample was available for only one of the patients. Serum samples were respectively tested for dengue-specific IgM and IgG antibodies using SD Dengue IgM and IgG Capture ELISA kits (Standard Diagnostics, Korea) [13]. Serum samples were also tested for dengue-specific NS1 antigen using both pan-E Early Dengue ELISA kit (Panbio, Australia) and Platelia Dengue NS1 Ag assay (Bio-Rad Laboratories, USA).

**Methods**

**Ethics Statement**

The study was approved by the University Malaya Medical Center (UMMC) Medical Ethics Committee (ethics committee/IRB reference number: 611.10). Informed consents were not obtained from the patients as this was a retrospective study.

**Clinical Case Definition**

The medical records of ten patients at UMMC with dengue-related deaths during the period from June 2006–October 2007 were reviewed and notes were transcribed into standardized data entry forms. Disease severity was classified following the WHO 1997 guideline [2]. This was done as the clinical notes were all in accordance to the WHO 1997 guidelines.

**Serology**

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**Virus Isolation and Genotyping**

Virus isolation was performed by inoculating the serum samples onto monolayer of Aedes albopictus C6/36 cells in 24-well plate. The cells were maintained in EMEM supplemented with 2% fetal bovine serum at 28°C for one week. RNA was extracted from cell culture supernatant using QIAamp Viral RNA Mini Kit (Qiagen, Germany). Genotyping was done using the in-house-developed multiplex RT-PCR genotyping kit which amplified a portion of viral NS3 gene. Amplification was performed as previously described [14,15].
chronic obstructive airway disease and obesity as the possible cause of death.

Dengue infection was confirmed in all patients by dengue serological tests. Seven were both IgM and IgG positive while three were IgM negative and IgG positive. Eight of the patients (two were unavailable) tested positive for dengue NS1 antigen with DENV-1 isolated from one case. The presence of anti-dengue IgG antibody concurrent with positive detection of dengue NS1 antigen confirmed secondary infections in eight patients. Of the eight patients, anti-dengue IgG titres in five patients were higher than IgM titres. Dengue NS1 antigen test was not performed in two cases (Patient 2 and 7). However, the presence of IgG in their serum within a period of less than two weeks since the onset of illness suggests secondary infection.

Discussion

The present study reviewed the clinical features of ten fatal cases of DHF/DSS seen at UMMC, a major teaching and referral hospital, during the period when Malaysia experienced dramatic increase in dengue cases. The dengue deaths were seen primarily in adult females and were associated with secondary dengue

Table 1. Demographics, co-morbidities, clinical features and postmortem findings of fatal dengue seen at UMMC between June 2006 to October 2007.

| Patient | Age/Sexa | Duration of illness prior admission/Duration of hospitalization (day) | Co-morbidities | Bleeding Manifestationc | Postmortem | Cause of deathd (as reviewed by the authors) |
|---------|----------|-------------------------------------------------|----------------|--------------------------|------------|-------------------------------------------|
| 1       | 12/F/C   | Unknown/0                                       | -              | petechiae at pleural surfaces, lung congestion and edema, large and granular liver, kidney with congested medulla, enlarged spleen; Histology: pulmonary hypertension (lungs) and severe fatty change in liver | -          | Unascertained; Postmortem: pulmonary hypertension due to chronic obstructive airway disease, obesity |
| 2       | 19/F/M   | 9/0                                             | -              | -                        | -          | DHF/DF                                    |
| 3       | 40/M/B   | 3/1                                             | newly diagnosed DM | petechiae                 | -          | DSS                                       |
| 4       | 34/F/M   | 3/1                                             | newly diagnosed DM; adrenal adenoma | petechiae, needle insertion site, RT, PV, PR | hemorrhage over hemispheres (brain) and septum (heart), pleural effusion and lung congestion, blood in stomach | DSS with ARF and severe bleeding |
| 5       | 39/F/M   | 4/1                                             | -              | petechiae, PR, PV, blood in NG tube, hematoma | -          | DSS, DIC, severe bleeding, MOF (ARF, ALF) |
| 6       | 42/F/I   | 5/1                                             | DM type 2      | -                        | pericardial and pleural effusion, hemorrhage over endocardium, fluid in peritoneal cavity and stomach, enlarged liver and spleen; Histology: severe lung congestion with intra-alveolar hemorrhage, spleen congestion, severe fatty infiltration in heart (suspecting of arrhythmogenic dysplasia), liver fatty change | DSS and severe bleeding |
| 7       | 18/F/I   | 6/3                                             | -              | petechiae                | -          | DSS with MOF (ARF, ARDS), coagulopathy and severe bleeding |
| 8       | 59/F/C   | 5/3                                             | -              | PR                       | -          | DSS complicated with cardiogenic shock secondary to myocarditis and pericarditis |
| 9       | 11/F/I   | 3/4                                             | -              | gums, blood stained ETT suctioning and coffee ground aspirate in NG tube | -          | DSS, APO during reabsorption phase. Septiceamic shock secondary to presumed HAP (Blood & BAL culture negative; severe lactic and metabolic acidosis). New CXR change. |
| 10      | 30/F/M   | 4/5                                             | -              | petechiae, GI, PV, PR, gum, epistaxis | -          | DSS with severe GI bleeding, MOF, DIC |

aSex- Female (F); Male (M).
bEthnicity- Malay (M); Chinese (C); Indian (I); Others, Bangladesh (B).
cBleeding Site- Bleeding per vagina (PV); Bleeding per rectum (PR); Gastrointestinal bleeding (GI); Respiratory tract (RT); Endotracheal tube (ETT); Nasogastric (NG).
dCause of death- Acute liver failure (ALF); Acute pulmonary oedema (APO); Acute renal failure (ARF); Multi-organ failure (MOF); Disseminated intravascular coagulation (DIC); Acute respiratory distress syndrome (ARDS); Hospital acquired pneumonia (HAP); Bronchoalveolar lavage (BAL); Chest X-ray (CXR).

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Majority of the patients presented with common clinical and laboratory warning signs of severe dengue before death. Underlying co-morbidities may be the contributing factors towards the rapid deterioration in severe dengue. Other complications included involvement of other organs including the brain, heart, liver and kidneys. This is reflective of the shift in the demographics of dengue cases in Malaysia where more adults are affected.

In Southeast Asia, severe and fatal dengue has been primarily described among children. Similar pattern was also observed in Malaysia until early 1982 [16,17,18,19] where the percentage of dengue cases became most common among adults of 13 to 35 years old. In UMMC, the median age of laboratory-confirmed dengue cases between the year 2006 to 2007 was 25 years (age range 1 month to 88 years). The majority of cases were adults of 21 to 25 years and >35 years old, with mean percentages of 20.5% and 23%, respectively (unpublished data). This trend is similar in most dengue endemic countries in Southeast Asia [20,21]. With this changing demography, it is possible that there are features of severe dengue leading to death that could be different from those seen in children.

In the present review, fatal cases comprised mainly of adults of >18 years old. There is a higher preponderance of fatal DHF/DSS amongst females. This is despite >55% of dengue cases seen at UMMC between the year 2006–2007 occurred in males (unpublished data). This observation is similar to that reported earlier where there was higher tendency of females to develop DHF/DSS [9,19] with higher mortality rate in females [22] even though males consistently comprised of the larger proportion of DF and DHF, especially in the <15 years age group [22,23]. More deaths among girls, especially those among the pediatric group, was also reported in Vietnam in 1996–2009, despite the predominance of boys in dengue cases [24,25]. Currently, there is no satisfactory explanation to this phenomena but there are suggestions that this may be due to the more robust immune response in females, resulting in females to be more prone to develop greater inflammatory response or higher susceptibility to capillary permeability [26,27]. There was no evidence of

### Table 2. Summary of clinical presentation in dengue fatal cases seen at UMMC between June 2006 to October 2007.

| Clinical Features                                | Symptoma | 2b | 3c | 4 | 5 | 6 | 7 | 8 | 9c | 10 | No. (%) |
|--------------------------------------------------|----------|----|----|---|---|---|---|---|---|----|---------|
| History of Fever/Chills/Rigors                    | ++       | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 9 (100) |
| Headache                                         |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 4 (44)  |
| Abdominal pain                                   |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 6 (67)  |
| Rash                                             |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 3 (33)  |
| Bodyache/Myalgia                                 | ++       | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 8 (89)  |
| Arthralgia                                        |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 3 (33)  |
| Vomiting/Nausea                                   | ++       | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 9 (100) |
| Diarrhea                                         |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 6 (67)  |
| Bleeding (Petechiae, Gum, Gl, PR, PV, etc)        | ++       | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 8 (89)  |
| Lethargy                                         |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 3 (33)  |
| Giddiness                                        |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 3 (33)  |
| Faint                                            |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 1 (11)  |
| Confused                                         |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 1 (11)  |
| Restless                                         |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 5 (56)  |
| Shortness of breath                               |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 4 (44)  |
| Signs                                            |          |    |    |    |    |    |    |    |    |    |         |
| Oliguria                                         |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 5 (56)  |
| Anuria                                           |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 3 (33)  |
| Dehydration                                      |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 6 (67)  |
| Ascites                                          |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 5 (56)  |
| Pleural effusion                                 |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 7 (78)  |
| Pericardial effusion                             |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 3 (33)  |
| Liver enlargement                                |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 3 (33)  |
| Tachycardia                                      |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 7 (78)  |
| Tachypnoe                                        |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 4 (44)  |
| Shock                                            |          | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | 7 (78)  |

*aBrought in dead;  
bMale;  
cChild.  
1Autopsy.  
Bleeding per vaginum (PV); Bleeding per rectum (PR); Gastrointestinal bleeding (GI).  
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differences in the susceptibility and severity to dengue between the different ethnic groups in Malaysia as the percentages of deaths paralleled the ethnic composition of patients who visited UMMC (unpublished data). This is similar to earlier findings done among the fatal cases in Singapore [28,29].

On average the patients in this review were admitted on day five of illness and most of them had defervesce. This was followed by rapid deterioration of clinical condition. Four patients died within 24 hours of admission and the remaining four died within 5 days of admission. Our observation is consistent with an earlier study done on seven dengue deaths in Singapore where the reported mean period of illness prior to hospitalization was 4.8 days. The mean duration of hospitalization before deaths, however, was longer at 13.7 days [29]. A study in Cuba with 12 fatal cases also reported worsening clinical condition and death occurring at an average of 2.9 days post-hospitalization, respectively [30]. However, the study reported hospitalization of patients at an average of 4.8 days prior to hospitalization and 7.5 days post-hospitalization, respectively [30]. Therefore, hematocrit may not be a sensitive marker of plasma leakage in dengue with severe bleeding. In our study, elevated liver enzymes were other important reported co-morbidities contributing to dengue fatalities [29,31,32,34,35] but these were not explicitly seen in our study.

Common clinical features of dengue seen in our study include general body ache, abdominal pain, plasma leakage, diarrhea, vomiting, dehydration and bleeding manifestations. Some of the symptoms are consistent with warning signs for severe dengue [3]. Similar findings, especially gastrointestinal symptoms have been reported in other studies [29,30,32] emphasizing the importance of warning signs as a tool to recognize patients at risk of severe dengue.

Hepatomegaly, a common and important clinical feature associated with DHF/DSS or severe dengue [36,37], was seen in four patients; two from physical examination and another two at postmortem. Hepatomegaly may have been an under-diagnosed clinical feature in our study possibly due to the insufficient documentation. The frequency of hepatomegaly may be higher as it was seen in two out of the three postmortem conducted. Hepatosplenomegaly is a clinical feature associated with macrophage activation syndrome (MAS) seen in many autoimmune diseases [38,39]. It may also be associated with DENV infection [40]. However, splenomegaly was not identified as a clinical feature in our series of patients and was only seen in two patients from their autopsy studies.

At least eight of the fatal cases in our study had evidence of secondary dengue infection, which has been associated with severe outcome of dengue via antibody-dependent enhancement (ADE) [41] and T cell original antigenic sin [42]. All our patients with results available had thrombocytopenia but only five had high hematocrit levels. Platelet count of less than 50 × 10^9/L concurrent with hemoconcentration has been shown to increase dengue mortality by six-fold [43]. Three patients (Patients 3, 4 and 7) had normal hematocrit levels despite clear evidence of severe plasma leakage. Patient 4 and 7 had clinical evidence of severe bleeding and Patient 3 may have occult bleeding. This may be the explanation for their ‘normal’ hematocrit levels at presentation. Therefore, hematocrit may not be a sensitive marker of plasma leakage in dengue with severe bleeding. In our study, elevated liver enzymes of >1000 IU/L was common. Equally common was

| Table 3. Laboratory diagnosis and hematological findings of samples from fatal dengue cases seen at UMMC between June 2006 to October 2007. |
|---------------------------------------------------------------|
| **Laboratory findings** | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** | **Patient 6** | **Patient 7** | **Patient 8** | **Patient 9** | **Patient 10** |
| Virus Isolation | — | — | — | — | — | — | — | — | — | — | — |
| NS1 antigen | — | — | N/A | — | — | — | N/A | — | — | — | — |
| Dengue IgM | — | — | — | — | — | — | — | — | — | — | — |
| Dengue IgG | — | — | — | — | — | — | — | — | — | — | — |
| Hemoconcentration | (hematocrit >20%) | N/A | — | — | — | — | — | — | — | — | — |
| Thrombocytopenia | (<50 × 10^9/L) | N/A | — | — | — | — | — | — | — | — | — |
| Prolonged APTT | (>38.9 secs) | N/A | — | — | — | — | — | — | — | — | — |
| Prolonged TT | (>19 secs) | N/A | — | — | — | — | — | — | — | — | — |
| Elevated AST | (>1000 IU/L) | N/A | — | — | — | — | — | — | — | — | — |
| Elevated ALT | (>1000 IU/L) | N/A | — | — | — | — | — | — | — | — | — |
| Increased Total Bilirubin | (>22 µmol/L) | N/A | — | — | — | — | — | — | — | — | — |
| Hypoalbuminemia | (<35 g/L) | N/A | — | — | — | — | — | — | — | — | — |

*+ = Positive; − = Negative; N/A = Not available.*  
Activated partial thromboplastin time (APTT); Thrombin time (TT); Alanine aminotransferase (ALT); Aspartate aminotransferase (AST).  
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In our study, decompensated DSS with evidence of massive plasma leakage, massive bleeding, MOF and coagulopathy were the primary cause of deaths. Per rectorum bleeding, vaginal bleeding and gastrointestinal bleeding were the commonest sites of severe bleeding. These observations are consistent with those reported in a number of other studies [30,50]. Here we also report hemorrhage over the brain hemispheres, the endocardium and septum of the heart and intra-alveolar demonstrated from autopsy. It has been suggested that several of these rare hemorrhagic manifestations has become more apparent and significant in DHF in the past 30 years and carries a higher risk of mortality [49,50].

The increasing reports of uncommon manifestations in dengue may be reflective of the shift in demographics where there is increasing incidence of DHF or severe dengue among the older age group of patients.

In conclusion, our study demonstrates a case series of severe dengue leading to death seen primarily in adult females with secondary dengue infection in Malaysia. The possible contributing role of underlying co-morbidities commonly seen in adults especially diabetes mellitus is highlighted. While most patients with fatal outcomes presented with common clinical and laboratory warning signs of severe dengue seen in all ages, the manifestation of uncommon clinical presentations of dengue is most likely a reflection of a change in the demographic pattern of the population being infected with dengue.

Supporting Information

Checklist S1 STROBE checklist. (DOC)

Author Contributions

Conceived and designed the experiments: SA. Performed the experiments: SSS BTT JAJ. Analyzed the data: SSS SFSO BTT JAJ SA. Contributed reagents/materials/analysis tools: SA. Wrote the paper: SSS SFSO BTA.

References

1. Guhler DJ (2012) The economic burden of dengue. Am J Trop Med Hyg 86: 743–744.
2. World Health Organization (1997) Dengue hemorrhagic fever: diagnosis, treatment, prevention and control. Geneva: World Health Organization.
3. World Health Organization (2009) Dengue guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization.
4. Rudnick A, Tan EE, Lucas JK, Omar MB (1965) Mosquito-Borne Hemorrhagic Fever in Malaya. Br Med J 1: 1269–1272.
5. Skau EM (1967) Dengue Fever in Penang. Br Med J 2: 1581–1582.
6. George R, Lam SK (1997) Dengue virus infection-the Malayali experience. Ann Acad Med Singapore 26: 815–819.
7. Abubakar S, Shafee N (2002) Outlook of dengue in Malaysia: a century later. Malaysia J Pathol 24: 31–37.
8. Parameswaran N (1965) Hemorrhagic fever in children in Penang, Med J Malaysia 29: 254–258.
9. Wallace HG, Lim TW, Rudnick A, Knudsen AB, Cheong WH, et al. (1980) Dengue hemorrhagic fever in Malaysia: the 1973 epidemic. Southeast Asian J Trop Med Public Health 11: 1–13.
10. George R, Kassim MS, Wah LT (1974) Mosquito-borne haemorrhagic fever. Med J Malaysia 29: 11–16.
11. World Health Organization Collaborating Centre for Arbovirus Reference and Research (Dengue/DHF). (2006–2007) Annual Report.
12. Guha-Sapir D, Schimmer B (2005) Dengue fever: new paradigms for a changing disease. Med Hyg 84: 127–134.
13. Wallace HG, Lim TW, Rudnick A, Knudsen AB, Cheong WH, et al. (1980) Dengue hemorrhagic fever in Malaysia: the 1973 epidemic. Southeast Asian J Trop Med Public Health 11: 1–13.
14. George R, Kassim MS, Wah LT (1974) Mosquito-borne haemorrhagic fever. Med J Malaysia 29: 11–16.
15. World Health Organization Collaborating Centre for Arbovirus Reference and Research (Dengue/DHF). (2006–2007) Annual Report.
16. Guha-Sapir D, Schimmer B (2005) Dengue fever: new paradigms for a changing disease. Med Hyg 84: 127–134.
32. Rigau-Perez JG, Laufer MK (2006) Dengue-related deaths in Puerto Rico, 1992–1996: diagnosis and clinical alarm signals. Clin Infect Dis 42: 1241–1246.
33. Anil NM, Paramesvarathy R, Tee GH, Gurpreet K, Karuthan C (2011) Prevalence of Chronic Illness and Health Seeking Behaviour in Malaysian Population: Results from the Third National Health Morbidity Survey (NHMS III). 2006. Med J Malaysia 66: 36–41.
34. Lee IK, Liu JW, Yang KD (2008) Clinical and laboratory characteristics and risk factors for fatality in elderly patients with dengue hemorrhagic fever. Am J Trop Med Hyg 79: 149–153.
35. Figueiredo MA, Rodrigues LC, Barreto ML, Lima JW, Costa MC, et al. (2010) Allergies and diabetes as risk factors for dengue hemorrhagic fever: results of a case control study. PLoS Negl Trop Dis 4: e659.
36. Nguyen TH, Le H, Tran TH, Lin TH, Nguyen K, et al. (2004) Dengue hemorrhagic fever in infants: a study of clinical and cytokine profiles. J Infect Dis 189: 221–232.
37. Thein TL, Gani VC, Lye DC, Yang CF, Lee YS (2013) Utilities and Limitations of the World Health Organization 2009 Warning Signs for Adult Dengue Severity. PLoS Negl Trop Dis 7: e2023.
38. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, et al. (2005) Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 146: 598–604.
39. Tan LH, Lum IC, Onar SF, Kan FK (2012) Hemophagocytosis in dengue: comprehensive report of six cases. J Clin Virol 55: 79–82.
40. Ray S, Kundu S, Saha M, Chakrabarti P (2011) Hemophagocytic syndrome in classic dengue Fever. J Glob Infect Dis 3: 399–401.
41. Halstead SB (2003) Neutralization and antibody-dependent enhancement of dengue viruses. Adv Virus Res 60: 421–467.
42. Mongkolosalaya J, Dejnirattisai W, Xia X, Vasanaowathana S, Tannwichanakit N, et al. (2003) Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever. Nat Med 9: 921–927.
43. Chua MN, Mokhada R, de Guzman M, Laberita F (1993) Prothrombin time and partial thromboplastin time as a predictor of bleeding in patients with dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 24 Suppl 1: 141–143.
44. Villar-Genzeno LA, Diaz-Quijano FA, Martinez-Vega RA (2005) Biochemical alterations as markers of dengue hemorrhagic fever. Am J Trop Med Hyg 78: 370–374.
45. De Rossi M, Bernasconi P, Baggi F, de Waal Malefyt R, Mantegazzra R (2000) Cytokines and chemokines are both expressed by human myeloblasts: possible relevance for the immune pathogenesis of muscle inflammation. Int Immunol 12: 1329–1335.
46. Salgado DM, Eliz JM, Mansfield K, Panqueba C, Castro D, et al. (2010) Heart and skeletal muscle are targets of dengue virus infection. Pediatr Infect Dis J 29: 230–242.
47. Witayathawornwong P (2005) Fatal dengue encephalitis. Southeast Asian J Trop Med Public Health 36: 200–202.
48. Lee IK, Lee WH, Liu JW, Yang KD (2010) Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients. Int J Infect Dis 14: e919–922.
49. Lee IK, Liu JW, Yang KD (2012) Fatal dengue hemorrhagic fever in adults: emphasizing the evolutionary pre-fatal clinical and laboratory manifestations. PLoS Negl Trop Dis 6: e1532.
50. George R (1992) Current status of the knowledge of dengue/DHF/DSS in Malaysia: Clinical Aspect. Phil J Microbiol Infect Dis 21: 41–45.