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Fatal dengue hemorrhagic fever in adults during a dengue epidemic in Singapore

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Summary
Background: Dengue fever has seen a significant re-emergence in Southeast Asia. Associated with the rise of dengue has been the increase in dengue-associated mortality. To better understand the predictors of mortality, we conducted a review of hospitalized adult dengue infections within our institution.
Methods: This was a retrospective case—control study of dengue-associated deaths at a large tertiary care hospital.
Results: In 2004, of 3186 cases of dengue fever (DF)/hemorrhagic dengue fever (DHF) admitted to our institution, there were 130 cases of DHF and seven dengue-associated deaths (case-fatality rate 5.4%). At least three of the seven fatal cases had serological evidence of primary dengue infection. All dengue-mortality cases had rapidly progressive clinical deterioration at an average of day 4 of fever with intensive care admission occurring on a mean of 5.6 days of fever. Adult respiratory distress syndrome, disseminated intravascular coagulopathy, and multi-organ failure were the most common causes of death despite early hospitalization, intravenous fluid, and blood-product support.
Conclusion: Dengue is associated with severe disease, and deaths do occur despite current supportive management. Fatal DHF/dengue shock syndrome (DSS) does occur in adults and in primary dengue infection. Better early predictors of disease severity and clinical interventions are needed.

Introduction

Dengue virus infection is an important and re-emerging infection in many parts of the tropics. Southeast Asia in particular has seen large epidemics of the disease in recent years with attendant mortality from dengue hemorrhagic fever and dengue shock syndrome. Over 250 000 cases of dengue hemorrhagic fever, mainly in children, are reported to the World Health Organization (WHO) annually, with mortality rates of 1—5% among patients with shock.[1]

In its severest form, dengue virus infection is associated with hemorrhagic complications, plasma leakage, shock,

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liver failure, and disseminated intravascular coagulopathy.[2] Unlike the epidemiology of dengue in many developing countries, the resurgence of dengue in Singapore has been associated with an adult predominance with very low incidence in children.[3] Dengue virus infections are rarely fatal in adults, although fatal infections do occur.[4]

Since 2003, dengue cases have risen dramatically in Singapore. In 2004, there was a record 9459 cases notified with eight deaths, with the highest incidence of disease in young adults aged 15–24 years.[5] More than three quarters of all dengue cases in Singapore are hospitalized.[5] In order to better understand the risk factors for mortality and the epidemiology of severe dengue cases in our hospital population, we conducted a case–control study of all dengue-associated deaths within our institution.

Methods

A retrospective case–control study was performed. All cases of dengue-associated mortality in Tan Tock Seng Hospital for the period 1 January to 31 September 2004 were identified through cross matching of hospital discharge data with dengue notification records. Notification of dengue infection to the Ministry of Health is mandatory in Singapore. The study was approved by the institutional review committee of the National Healthcare Group. Tan Tock Seng Hospital (TTSH) is a 1100-bed tertiary care adult hospital serving the central, north, and northeastern adult population of Singapore – areas of known high dengue transmission.[5]

All cases of dengue were defined as: (i) a compatible clinical illness with (ii) positive serology (IgM and/or IgG by Dengue Duo Rapid Strip Test, PanBio, Australia)[6] or reverse transcriptase-polymerase chain reaction (RT-PCR) test. Dengue-associated deaths were defined as deaths resulting from, and as a direct consequence of, acute dengue infection. Persons admitted with dengue virus infection during the same month of admission as dengue-associated death cases were randomly selected from the hospital patient database as controls. Five controls were chosen for every dengue-associated death case. The medical records of all cases identified were reviewed. Final disease categorization into dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) was based on the World Health Organization's recommended system of classification.[7] Day of illness at admission (day 1 of illness was counted as the day

Table 1 Admission characteristics of mortality-associated dengue cases and those with uncomplicated dengue fever

Variable	Mortality-associated group (n = 7)	Uncomplicated DF (n = 35)	p
Males (%)	5 (71.4)	28 (80.0)	NS
Mean age (years)	47	24	NS
Underlying disease			
Diabetes (%)	1 (14.3)	2 (5.7)	NS
Hypertension (%)	1 (14.3)	1 (2.9)	NS
Ethnicity			NS
Chinese (%)	4 (57.1)	30 (85.7)	
Malay (%)	2 (28.6)	1 (2.9)	
Indian (%)	1 (14.3)	2 (5.7)	
Others (%)	0	2 (5.7)	
Foreign born (%)	1 (14.3)	3 (8.6)	NS
Duration of fever (days)	4.8	4.8	NS
Primary dengue (%)*	3/4 (75.0)	24/31 (77.4)	NS
Minor bleeding (%)	3 (42.9)	5 (14.3)	0.084
Diarrhea (%)	2 (28.6)	9 (25.7)	NS
Headache (%)	1 (14.3)	15 (42.9)	NS
Abdominal pain (%)	4 (57.1)	13 (37.1)	NS
Nausea and vomiting (%)	4 (57.1)	20 (57.1)	NS
Confusion (%)	2 (28.6)	0	0.019
Rash (%)	0	17 (48.6)	0.039
Heart rate on admission (beats/min)	122	83	<0.05
Pulse pressure on admission (mmHg)	47	49	NS
Platelet count ($\times 10^9$ cells/L)	71	76	NS
Hematocrit (%)	45.6	43.8	NS
AST (IU/L)	1293	196	0.015
ALT (IU/L)	309	132	0.075
Albumin (g/L)	32.4	41.3	<0.05
Creatinine (μmol/L)	114	79	0.008
APTT (s)	50.7	47.9	NS
PT (s)	18.2	12.7	<0.05

AST, aspartate aminotransferase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; PT, prothrombin time.
* Data not available for all patients.

Table 2 Demographic and clinical features of dengue mortality cases

Case	Age (years)/sex	Fever duration prior to admission (days)	Co-morbidities	Dengue tests	Clinical course	Duration of hospitalization (days)	Complications/cause of death
1	51/F	3	Diabetes mellitus; hypertension	IgM pos; IgG neg	Admitted in extremis	3	Gastrointestinal bleeding; ketoacidosis; multi-organ failure
2	31/F	7	Nil	IgM pos; IgG neg	Rapidly progressive hypoxemia and hypotension	4	Acute respiratory distress syndrome; myocarditis with cardiogenic shock
3	47/M	Unknown	Diabetes mellitus	IgM pos; IgG neg	Acute confusion and stroke; rapid deterioration; prolonged ICU stay	30	Gram-negative septicemia; acute respiratory distress syndrome; cerebral infarction; myocarditis with cardiogenic shock
4	56/M	4	Hyperthyroidism	PCR pos	Rapid with bleeding (GI) and shock; prolonged ICU stay	33	Gastrointestinal bleeding; acute respiratory distress syndrome; septicemia; multi-organ failure
5	52/M	3	Nil	PCR pos	Rapid with bleeding (GI) and shock	2	Disseminated intravascular coagulopathy; multi-organ failure
6	22/M	7	Nil	PCR pos	Rapid with bleeding (GI/lung) and shock	2	Severe bilateral pneumonia; disseminated intravascular coagulopathy; multi-organ failure
7	71/M	Unknown	Nil	PCR pos; IgM and IgG pos	Acute stroke with prolonged ICU stay	22	Acute renal failure; acute respiratory distress syndrome; septicemia; multiple cerebrovascular accidents

ICU, intensive care unit; GI, gastrointestinal.

of fever onset), demographic, clinical, and laboratory data were collected on standardized data-collection forms. Petechiae, epistaxis, gingival bleeding, or menorrhagia were classified as minor bleeding complications.

Statistical analysis

The Student's *t* test was used for comparison of continuous variables, and Fisher's exact test was used for comparison of dichotomous variables of mortality-associated dengue cases and those with uncomplicated DF. For data that were not normally distributed, the Mann—Whitney U test for continuous values was used. Variables found to be statistically significant in univariate analyses were entered into multivariate analysis using a logistic regression model to identify independent risk factors for mortality. A two-tailed p value of <0.05 was considered statistically significant.

Results

A total of 3186 cases of DF/DHF were admitted to TTSH during the study period. Of these, 130 (4.1%) were diagnosed with DHF with seven dengue-associated deaths (case-fatality rate 5.4%).

The admission characteristics of the dengue-associated death cases compared to controls are shown in Table 1. All controls were classified as having uncomplicated dengue fever. Of the dengue-associated death cases, five (71.4%) were male with a mean age of 47 years (range: 22—71); four patients (57.1%) were Chinese, two Malay (28.6%), and one Indian (14.3%). The main presenting complaint in all these patients was fever; other symptoms included confusion (28.6%), bleeding manifestations (gum bleeding, hematochezia) (42.9%), nausea and vomiting (57.1%), and abdominal pain (57.1%). Two patients (patients 3 and 7, Table 2) presented chiefly with neurological symptoms (localized weakness, confusion) and fever and had initial admitting diagnoses of cerebrovascular accidents. Two patients (patients 4 and 6) had fever, abdominal pain, and diarrhea as predominant symptoms and were admitted initially as infective gastroenteritis cases. Patient 1 was diabetic and presented in ketoacidosis. In four cases (57.1%), prominent abdominal pain and persistent vomiting preceded hypotension and clinical deterioration. No rash was noted in any of the cases at presentation. Three patients (42.8%) had pre-existing co-morbidities including diabetes, hypertension, and hyperthyroidism. The mean number of days of illness prior to hospitalization was 4.8.

On admission, all dengue-associated death patients were febrile (mean 38.7 °C) and tachycardic. Blood pressure was low (SBP <100 mmHg) in only one patient and all had normal pulse pressure (>20 mmHg). Laboratory abnormalities on admission included: thrombocytopenia (71.4%; mean platelet count 71×10^9/L), coagulopathy (42.9%), leukopenia (28.6%), raised ALT or AST >3 times above normal (85.7%). Chest X-rays were abnormal in five cases (71.4%) with all showing bilateral interstitial patterns of disease. Dengue diagnosis was confirmed by PCR in four patients (serotype unavailable); dengue serology was performed in four patients, three with positive IgM alone and one with both positive IgG and IgM, consistent with primary and secondary dengue infection respectively (Table 2).[6] Three patients were directly admitted to the intensive care unit (ICU). Clinical deterioration after admission was rapid in all cases and all patients required eventual transfer to the ICU within a mean of 2.4 days post-admission and at 5.6 days of fever. Transfer to the ICU was for hypotension in five patients (71.4%) and respiratory failure in two (28.6%). All patients received platelet and/or blood product transfusions. Two patients had evidence of depressed cardiac function (ejection fractions <30%) on bedside echocardiography. Causes of death in this series were: multi-organ failure with adult respiratory distress syndrome (57.1%), pneumonia and/or septicemia (57.1%), intracerebral hemorrhage (14.3%). No autopsy data were available.

On univariate analysis, confusion, absence of rash, tachycardia, and abnormalities in liver transaminases, creatinine, albumin, and prothrombin time were statistically more frequent in mortality-associated cases. On multivariate analysis, only tachycardia on admission was found to be independently associated with dengue mortality (OR = 3.56, 95% CI = 2.76—4.87, $p = 0.036$).

Discussion

This series of cases serves to characterize the mortality associated with adult dengue virus infection during an epidemic outbreak. Often considered more common in children, DHF is now being seen more frequently in older adults as a consequence of shifting patterns of infection and immunity.[4,8,9] Although the pathogenesis and pathophysiology of severe dengue infections remains incompletely understood, possible contributory factors to increased disease severity have been described. Age,[10] sex,[4] race,[11] pre-existing co-morbidities,[12] and viral-specific features[13] have been noted to play a role in disease outcomes by various authors. Vaughn and colleagues have previously shown that disease severity correlates to high dengue viremia titers and secondary infections.[14]

It is postulated that the sequence of infecting dengue virus serotypes may be significant with respect to the risk of developing DHF and more severe disease,[15,16] though all four dengue serotypes can cause DHF.[17] In 2003, DEN-2 was the predominant circulating strain in Singapore (80% of serotypes detected; overall dengue incidence 108.5 per 100 000 with six deaths);[5] however 2004 saw the introduction of DEN-1 as the major serotype and a resurgence of dengue (67% of circulating strains tested; overall dengue incidence 223 per 100 000 with eight deaths).[18] It is possible that this change in the predominant dengue strain and/or sequence of infections contributed towards the increase in DHF and more severe outcomes seen, though this remains unproven. Further, at least three of the fatal cases in this series had evidence of primary dengue infection on serology. This is in contrast to other reports that have described mortality and severe disease occurring predominantly in secondary infection.[4,11,16,19]

The mortality rate in cases complicated by hemorrhage is three to four times greater than that in those without bleeding manifestations.[7] Mortality is usually linked to delayed provision of supportive treatment and/or pre-morbid chronic illness.[7] In this series, though the average duration of illness prior to admission and presence of co-morbidities was not signifi-

cantly different from controls, most patients had a fulminant course or presented at a far advanced stage of illness. Clinical deterioration occurred on average at day 4 with patients entering the intensive care unit at a mean of day 5.6 of fever. This clinical course is similar to that classically described in DHF/DSS[7,19] and in other series on adult dengue mortality.[4,8,20]

Although good early predictors of severity are presently lacking, warning symptoms such as abdominal pain and vomiting were noted in the majority of the severe cases prior to clinical deterioration. This is a well-recognized feature of severe plasma leakage and impending shock and when it occurs around the period of fever defervescence, should prompt closer monitoring and treatment.[7] Further, the prolongation of prothrombin time (PT) seen in mortality-associated cases in this series is consistent with the coagulopathy and abnormalities in the tissue-factor pathway seen in severe dengue cases[21–23] and should warrant prompt correction and support. Autopsy studies demonstrate that patients who succumb to DHF do so from acute physiologic reactions caused by vascular permeability and inflammation.[20,24] The mainstay of treatment remains prompt fluid resuscitation to counteract massive plasma leakage. Timely and effective intravenous crystalloid replacement of plasma losses results in a favorable outcome in most cases.[25,26] Reversing shock and electrolyte abnormalities help prevent the onset of disseminated intravascular coagulation.[7] However the use of preventive blood transfusion in DHF/DSS especially during the plasma leakage phase may be deleterious[27] and might contribute to increased incidence of pulmonary edema and congestive heart failure. Its routine role in the clinical management of severe dengue infection merits further study and review.

As this series demonstrates, fatal DHF/DSS does occur in adults and in primary dengue infection. A minority of patients will still progress into fatal DHF/DSS and intractable coagulopathy despite receipt of current supportive measures, highlighting the need for improved clinical interventions and early predictors of disease severity.

Conflict of interest: No conflict of interest to declare.

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