International Journal of Infectious Diseases (2007) 11, 263—267

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

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Received 26 October 2005; received in revised form 16 February 2006; accepted 22 February 2006
Corresponding Editor: Jane Zuckerman, London, UK

KEYWORDS
Dengue;
Adults;
Mortality;
Epidemiology

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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1201-9712/$32.00 © 2006 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.
doi:10.1016/j.ijid.2006.02.012

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.