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Risk factors of mortality among dengue patients admitted to a tertiary care setting in Kerala, India

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Abstract Dengue is one of the most serious and rapidly emerging tropical mosquito-borne diseases. The state of Kerala in India is hyperendemic for the disease and is one of the leading states in the reporting of deaths due to dengue. As primary prevention of dengue has had limited success, the prevention of mortality through the identification of risk factors and efficient patient management is of utmost importance. Hence, a record-based case control study was conducted in the Medical College Hospital in Thiruvananthapuram to identify the risk factors of mortality in patients admitted with dengue. Dengue patients over 40 years of age were 9.3 times (95% CI; 1.9—44.4) more likely to die compared with younger patients. The clinical features associated with mortality from dengue were altered sensorium (odds ratio (OR) — 156, 95% CI; 12.575—1935.197), abnormal reflexes (OR — 8.5, 95% CI; 1.833—39.421) and edema (OR — 13.22, 95% CI; 2.651—65.951). Mortality was also higher in those patients with co-morbidities such as diabetes mellitus (OR — 26, 95% CI; 2.47—273.674) and hypertension (OR — 44, 95% CI; 6.23—315.499). The independent predictors of mortality were altered sensorium and hypertension. Dengue fever patients with these clinical features and those who are elderly should be more rigorously monitored and promptly referred from lower settings when required to reduce mortality.

Introduction

Dengue is one of the most serious and rapidly emerging tropical mosquito-borne diseases. The global disease burden is 465,000 Disability adjusted life years DALYs, which is only paralleled by that of malaria among mosquito-borne diseases [1]. Worldwide, approximately 2.5—3 billion people (40% of the global population) live in constant risk of contracting this infection. It is estimated that 50 million cases and 24,000 deaths occur annually in 100 endemic countries worldwide. Nearly 500,000 cases are hospitalized annually, of which 90% are

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children. The south-east Asia region contributes 52% of the cases annually. India is one of the seven identified countries in this region that regularly reports dengue fever/dengue hemorrhagic fever (DF/DHF) outbreaks. India appears to be transforming into a major hyperendemic niche for dengue infection. Increasingly, previously unaffected areas are being struck by the dengue epidemic. The first confirmed report of dengue infection in India dates back to the 1940s. Thereafter, several states began to report the disease, which mostly struck in epidemic proportion, often inflicting heavy morbidity and mortality, both in urban and rural environments [2,3].

In Kerala, cases of dengue, including some deaths, were reported for the first time in 1997; nevertheless, DEN-1, DEN-2 and DEN-4 viruses had been previously detected in human sera. Dengue antibodies had been detected in human sera from Kozhikode, Kannur, Palakkad, Thrissur, Kottayam and Thiruvananthapuram districts as early as 1979 [4]. In recent years, DEN-2 and DEN-3 have been isolated from vector mosquitoes and human blood sera, respectively [5]. In 2003, Kerala reported the highest number of deaths due to dengue among Indian states, and over the years, the reported cases of dengue in this region have been increasing [6]. The proportion of deaths contributed by Kerala has also increased from 8% in 2006 to 15% in 2010. Kerala is now hyper-endemic for dengue, with the presence of all four serotypes, high rates of co-infection and local genomic evolution of viral strains [7]. The district of Thiruvananthapuram has reported the greatest number of cases in the state; 40—50% of the cases reported in Thiruvananthapuram are from the urban areas of the district [6].

Death due to dengue is an avoidable cause of mortality [8]. The primary prevention of dengue through vector control activities has had limited success worldwide [9]. Currently, there is neither a vaccine to prevent the disease nor an antiviral treatment. However, secondary prevention to reduce mortality through improved clinical case management has substantially lowered the mortality rate for severe dengue over the past two decades from 10—20% to <1% [10,11]. The first objective of the WHO global strategy 2012—2020 is to reduce the mortality due to dengue by 50% from 2010 levels [12]. The number of deaths is determined not only by the factors that facilitate transmission but also by those that influence the severity of the disease and the ease of health care access [13]. Dengue mortality can be reduced by the implementation of early case detection and appropriate management of severe cases. Research to provide better diagnostics and biomarkers that can predict disease severity is urgently needed [12]. Organ involvement, shock, bacteremia, co-morbidities, hemorrhage and certain biochemical parameters have been identified as useful predictors of mortality in studies conducted in dengue-endemic countries, but there may be regional differences. The objective of this study was to identify the risk factors of mortality in dengue patients admitted to the Medical College Hospital, Thiruvananthapuram during the period 2005—2008.

Materials and methods

Study design

A case control study was conducted using the hospital records of dengue patients admitted to the Medical College of Thiruvananthapuram during the period 2005—2008.

Setting

Medical College Hospital, located in Thiruvananthapuram, Kerala, India, is a premier institution for the provision of comprehensive tertiary health care irrespective of economic or social status and disabilities. It is the largest multi-specialty hospital in South Kerala and serves the major portion of the Thiruvananthapuram and Kollam districts and the adjacent districts of Tamil Nadu.

Study population

A case was defined as a patient who was admitted with a diagnosis of probable dengue confirmed by either reverse transcriptase polymerase chain reaction (RT-PCR) or IgM antibody and who died during the hospital stay. The controls were dengue-confirmed patients who recovered from the illness during their stay in the hospital and were subsequently discharged.

Sample size and sampling technique

There were only 10 confirmed dengue deaths during 2005—2008 that met the eligibility criteria; these were selected as the cases. The patients who met the criteria for controls were enlisted, and then 40 individuals were randomly selected from this list.

Data collection

A semi-structured questionnaire was used to collect the study variables. The study variables included

socio-demographic characteristics, such as age and sex, and clinical details, including the presence of fever and associated symptoms, such as headache, arthralgia, myalgia, retro-orbital pain, cough, anorexia, constipation, loose stools, sore throat, rash, vomiting, restlessness, abdominal pain and decreased urine output. Important clinical signs such as altered sensorium, abnormal reflexes, ascitis, bleeding manifestations, pallor, icterus, edema, hypotension and circulatory failure were also collected. The presence of co-morbidities such as diabetes mellitus, hypertension, coronary artery disease, tuberculosis, liver problems and renal problems were also taken as variables. The history of previous dengue infection and habits such as smoking and alcoholism were assessed. Biochemical parameters were also considered, including hemoglobin, total cell count, ESR, platelet count, electrolyte imbalance, liver function and renal function. Thrombocytopenia was defined as a platelet count less than 100,000 at any point during the course of illness. The adequacy of vital sign and temperature monitoring was also assessed. We also searched for the presence of complications such as shock and any delay in seeking treatment.

Study period

The records of dengue cases and deaths during the period 2005—2008 were studied.

Statistical analysis

Data entry and analysis were completed in SPSS version 11.0. Chi-square tests and Fisher's exact tests for qualitative variables were used for the bivariate analysis. The quantitative variables were categorized using the appropriate cut-off points and medians. Logistic regression, employing the maximum likelihood method, was used for the multivariate analysis in SPSS. To overcome the limitation of a small sample size, a logistic regression was also performed in '*R*' using the penalized likelihood method/Firth method for fitting the final model. Collinearity between the predictor variables included in the model was ruled out by performing collinearity diagnostics in SPSS, analysing the variance inflation factor, tolerance and standard error of beta.

Ethical considerations

Approval for the study was obtained from the hospital superintendent, the officer in charge of the record library and the heads of the departments of medicine and community medicine. Clearance from the institutional ethics committee was also obtained.

Table 1 Age and sex of the study subjects.

Age	Sex		Total
	Male	Female	
Age < 40 years	8 (27.6%)	7 (33.3%)	15 (30.0%)
Age > 40 years	21 (72.4%)	14 (66.7%)	35 (70.0%)
Total	29 (100%)	21 (100%)	50 (100%)

Results

There were 5 male and 5 female deaths. The age and sex composition of the study subjects is displayed in Table 1. Age >40 years was found to be a risk factor for mortality ($p = 0.002$). Seventy percent of the cases were above 40 years of age, as compared to 20% of the controls. Those above the age of 40 years were 9.3 times (95% CI; 1.9—44.4) more likely to die if affected by dengue (Table 3). The mortality rate was higher in females (23.8%) than in males (17.2%).

The most common symptoms among all patients, in addition to fever were myalgia, hemorrhagic manifestations and vomiting, which were observed in 58%, 36% and 32% of the patients, respectively. The most common symptom in the survivors was myalgia, whereas hemorrhagic manifestations were the most common symptoms among those who died of dengue. Among the symptoms assessed, chills, constipation, abdominal pain, bleeding, decreased urine output and restlessness were found in a higher percentage of the cases than in the controls (Table 2). However, these differences were not statistically significant.

Among the signs assessed, altered sensorium, abnormal reflexes and edema were significantly associated with mortality. Pallor was not associated with mortality, but lower hemoglobin values were ($p = 0.045$). Those with co-morbidities such as diabetes mellitus and hypertension had a higher risk of mortality than those who did not (Table 3). Coronary artery disease (2%), a history of tuberculosis (3%), liver disease (14%) and renal problems (2%) were observed in the study subjects but were not associated with mortality. A higher percentage of the controls were smokers (15% vs. 10%) and alcoholics (10% vs. 0%) compared with the cases. No significant relation was found between mortality and these behaviors.

Leucopenia was observed in 33 (66%) dengue patients, and thrombocytopenia was present in

Table 2 Comparison of Symptoms among cases and controls.

Symptoms	Case $N = 10$ frequency (%)	Control $N = 10$ frequency (%)	Total
Chills	3 (30.0)	9 (22.5)	12 (24.0)
Arthralgia	1 (10.0)	8 (20.0)	9 (18.0)
Myalgia	3 (30.0)	26 (65.0)	29 (58.0)
Retro-orbital pain	0	4 (10.0)	4 (8.0)
Cough	2 (20.0)	10 (25.0)	12 (24.0)
Anorexia	1 (10.0)	4 (10.0)	5 (10.0)
Constipation	1 (10.0)	2 (5.0)	3 (6.0)
Loose stools	1 (10.0)	4 (10.0)	5 (10.0)
Abdominal pain	2 (20.0)	7 (17.5)	9 (18.0)
Sore throat	0	2 (5.0)	2 (4.0)
Rash	1 (10.0)	13 (32.5)	14 (28.0)
Vomiting	2 (20.0)	14 (35.0)	16 (32.0)
Bleeding	4 (40.0)	14 (35.0)	18 (36.0)
Decreased urine output	3 (30.0)	4 (10.0)	7 (14.0)
Headache	0	10 (25.0)	10 (20.0)
Restlessness	1 (10.0)	0	1 (2.0)

41 (82%) dengue patients. A higher proportion of patients who died had thrombocytopenia compared to the survivors. Platelet count returned to normal at the time of discharge in 65% of the survivors, while none of the people who died had a return of platelet count to normal. Half of the patients had electrolyte imbalance. Abnormal liver function test values were found in a higher proportion of patients who died compared with survivors, although the difference between the two groups was not statistically significant (Table 3). Vital signs were adequately monitored in 92% of the admitted patients, whereas temperature monitoring was satisfactory in only 58% of them. There were no differences in monitoring between the cases and the controls.

In the logistic regression using the maximum likelihood method, the independent predictors of mortality were altered sensorium ($p = 0.002$) and hypertension ($p = 0.03$). The adjusted odds ratios for altered sensorium was 97.3 (95% CI; 5.3—1778.0), and that for hypertension was 24.1 (95% CI; 1.4—412.9). To reduce the bias of small sample size, the penalized likelihood method was performed in *R*, which yielded the same predictors of mortality, namely, altered sensorium ($p = 0.0003$) and hypertension ($p = 0.02$).

Table 3 Features associated with dengue mortality.

	Case $N = 10$ frequency (%)	Control $N = 40$ frequency (%)	*p*-Value	Odds ratio (95% CI)
Age > 40 years	7 (70)	8 (20)	0.002	9.3 (1.9—44.4)
Abnormal reflex	6 (60)	6 (15)	0.007	8.5 (1.8—39.4)
Altered sensorium	8 (80)	1 (2.5)	0.000	156 (12.6—1935.2)
Ascites	0 (0)	4 (10)	0.3	
Hypotension	6 (60)	15 (37.5)	0.2	2.5 (0.6—10.3)
Pallor	2 (20)	2 (5)	0.1	4.8 (0.6—38.9)
Edema	7 (70)	6 (15)	0.001	13.2 (2.6—65.9)
Diabetes mellitus	4 (40)	1(2.5)	0.004	26 (2.5—273.7)
Hypertension	7 (70)	2 (5)	0.000	44.3 (6.2—315.5)
Leucopenia	6 (60)	27 (67.5)	0.7	0.7 (0.2—3.0)
Elevated ESR	3 (30)	17 (42.5)	0.5	0.6 (0.1—2.6)
Thrombocytopenia	10 (100)	31 (77.5)	0.09	1.7 (1.2—2.4)
Platelet returned to normal	0 (0)	26 (65.0)	0.000	
Electrolyte imbalance	4 (40)	21 (52.5)	0.5	0.6 (0.1—2.5)
Abnormal LFT	4 (40)	9 (22.5)	0.3	2.3 (0.5—9.9)
Anemia	7 (70)	14 (35.0)	0.045	4.3 (1.0—19.4)

Discussion

An important determinant of mortality identified in our study was age greater than 40 years. The risk of mortality due to dengue is higher in the elderly [14]. A study in Brazil found that dengue patients who were 50 years of age and above had a 2.3-fold higher chance of mortality than younger patients [1]. In older patients, constitutional symptoms are less likely, while multiorgan involvement and bacteremia are more likely, possibly because longer periods of hospitalization are more common in this age group [14,15]. Acute renal failure has a poor prognosis in the elderly with dengue infection [16].

In two studies, females had higher rates of mortality due to dengue: in the first study, girls had a higher risk of mortality (OR — 1.57, 95% CI — 1.1—2.2) [17], and in the second study, adult females constituted 90% of the deaths [18]. The greater mortality in females may be due to their more robust immune response, making them more prone to developing a greater inflammatory response or higher susceptibility to capillary permeability [18,19].

The presence of altered sensorium and abnormal reflexes is indicative of CNS involvement. As evidenced in this study and suggested in several other studies, brain involvement is associated with a higher incidence of mortality in dengue patients. Encephalopathy may be due to acute liver failure from hepatitis [20]. Encephalitis may also be due to the neurotropic effect of the virus [21] or to secondary bacterial infections [22]. Coma on presentation [23] and impaired consciousness are associated with high mortality and multi-organ involvement [21,24]; in one study, impaired consciousness was found in 57.1% of dengue deaths [25]. The occurrence of seizures is another neurological sign associated with higher mortality [23,26]; in one study, seizures were documented in 33% of the dengue deaths [26].

Hemorrhagic manifestations were common among those patients who died from dengue in our setting. Other studies have also showed that hemorrhagic complications, such as epistaxis, gingival bleeding, gastrointestinal bleeding, hematuria and hypermenorrhea, although rare, are an important cause of death in dengue [27]. In our study, abdominal pain was more frequent in the cases than in the survivors; this symptom has been identified as an early warning symptom, along with persistent vomiting, and is one of the warning signs of dengue according to the WHO 2009 case definition [28,29].

Another important determinant of mortality identified in several studies is the presence of co-morbidities. Dengue patients with diabetes mellitus [16,30], hypertension, chronic anemia, congestive heart failure, other cardiovascular diseases, chronic obstructive pulmonary disease, asthma, renal disease and multiple co-morbidities were found to have a higher incidence of mortality [14,25,26,30—34]. Our study adds to this evidence. The presence of acquired co-morbidities such as obesity [26], smoking and alcoholism was also associated with higher mortality [34,35]. A relation between dengue death and smoking was not found in our study.

Platelet counts may be predictors of mortality. Thrombocytopenia was present in all of the patients who died of dengue. The risk of death was 6 times greater in those with a platelet count <50,000/μl in the pediatric population [36]. Prolongation of prothrombin time has been associated with higher fatality [36].

Performing concurrent assays for dengue virus non-structural protein 1 (NS1), anti-dengue IgM and anti-dengue IgG along with platelet enumeration in the 'Dengue Package' is immensely beneficial for patients, clinicians and public health officials. The 'Dengue Package' produces an earlier differential diagnosis in suspected cases and early detection of thrombocytopenia, enabling appropriate intervention and prevention of death [37].

Higher blood urea nitrogen (uremia), lower bicarbonate (acidosis), higher APTT and higher SGPT, SGOT >300 mg/dl [22] are also associated with mortality in dengue. Elevated liver transaminases and hypoalbuminemia could be good indicators of vascular leakage or hepatic dysfunction in DHF and could be used to identify cases of severe dengue [38]. A hemoglobin value of less than 9 mg/dl was associated with a 4-fold higher risk of mortality and/or severity [39]. Because pallor was not associated with mortality in our study, it may be inferred that the subjective nature of this assessment could contribute to errors; therefore, it is advisable to check the hemoglobin level of all dengue patients. In our study, abnormal LFT was higher among the patients who died of dengue. However, the failure to obtain a statistical significance could be attributed to the small sample size, which is a major limitation of the study and is the reason for the wide confidence intervals. As the case fatality rates of dengue are low, especially in tertiary care settings with good management, we could obtain only a small number of cases. Another drawback of the study is that the study was retrospective in nature and used only information that was recorded in the case sheets. Therefore, certain

crucial determinants of mortality, such as serotype, could not be studied.

Conclusions

Patients with dengue fever who have altered sensorium, abnormal reflex, edema, diabetes mellitus, hypertension and persistently low platelet count have a higher risk of mortality. At primary and secondary levels of health care delivery, patients with these symptoms must be promptly referred. At tertiary levels, dengue patients with these clinical features should be given extra care and monitored more rigorously so that mortality can be decreased. Special care and attention should be given to the elderly at all levels of healthcare to reduce mortality.

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Competing interests

None declared.

Ethical approval

Not required.

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