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Predictors of severe manifestations in a cohort of adult dengue patients

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ABSTRACT

Background: Key symptoms observed during the febrile phase of dengue may identify patients who are likely to progress to severe disease.
Objectives: To test this hypothesis, we examined the relationships between symptoms reported by patients at presentation and the development of severe outcomes.
Study design: Retrospective analysis of data recorded prospectively in 560 adult dengue patients admitted to an emergency department. A logistic regression analysis was used to quantify the association between symptoms reported at presentation and outcome.
Results: Plasma leakage was observed in 95 patients (17%), severe thrombocytopenia (platelet counts $<20 \times 10^9$/L) in 93 patients (16.6%) and acute hepatitis in 42 patients (7.5%). Severe thrombocytopenia developed in 57% of patients with plasma leakage and 40.5% of patients with hepatitis. Patients who developed a plasma leakage syndrome were older, mainly male, and reported more often an abdominal pain and a cough. Diarrhea and taking paracetamol >60 mg/kg/day before admission were associated with the development of acute hepatitis. Seven patients died. The mortality rate was 6/95 (6.3%) in patients who developed plasma leakage, 3/42 (7.1%) in patients who developed hepatitis, 5/93 (5.4%) in patients with severe thrombocytopenia, and 3/12 (25%) in the patients who demonstrated together all these severe manifestations.
Conclusion: Plasma leakage, severe thrombocytopenia and acute hepatitis identified subgroups of adult dengue patients with increased mortality rates. Key symptoms reported by the patients at presentation such as abdominal pain, cough or diarrhea were significantly associated with the development of severe manifestations and should be considered as warning signs.

1. Background

Since its first descriptions about 40 years ago, dengue fever with its clinical presentation has been extensively described in the medical literature.[1] Although most infections are asymptomatic or associated with minor illness, millions of people across the tropical and subtropical world develop overt clinical forms of dengue infections every year. When symptomatic, the clinical presentation of dengue ranges from a non-specific, acute febrile illness which lasts for less than 1 week (classical dengue fever—DF) to severe forms of dengue hemorrhagic fever (DHF), as described in the World Health Organization (WHO) classification system. The central pathophysiological feature that distinguishes DF from DHF is a transient increase in vascular permeability which may lead to the life threatening dengue shock syndrome (DSS).[1] The progression of illness to DHF/DSS may develop within 3–5 days following an undifferentiated symptomatic febrile phase. Typically, development of signs and symptoms of plasma leakage coincide with defervescence, as demonstrated by the occurrence of serous effusions in the pleural and peritoneal spaces, elevation of hematocrit and hypoalbuminemia. Liver enlargement, bleeding, and thrombocytopenia are other typical features of the progression of illness to DHF. In the most severe cases, signs of circulatory failure develop indicating

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Table 1
Clinical characteristics and basic symptoms observed in adult dengue patients on admission time in the emergency room according to outcome features.

Patients demographics and basic symptoms	Uncomplicated dengue fever, $n=277$	Platelet counts $<20\times10^9$/L, $n=93$	Plasma leakage, $n=95$	Acute hepatitis, $n=42$
Age (years)[a]	29 (14–78)	45.5 (16–83) (c)[b]	43.5 (16–83) (c)	39 (14–63) (a)
Male to female ratio	0.63	1.54 (c)	2.92 (c)	1.21
DENV-2 (%)	61.7	72.3	74.5	71.4
Secondary dengue (%)	39.6	66.7 (c)	68.2 (c)	79.5 (c)
Hospitalized (%)	8.5	75.5 (c)	80.9 (c)	57.1 (c)
Headache (%)	88.1	83	74.5 (b)	78.6
Myalgia (%)	80	79.6	75.5	76.2
Arthralgia (%)	58.7	63.7	58.2	58.5
Back pain (%)	76.1	70.2	72.3	64.3
Intense asthenia (%)	58.6	76.9 (b)	79.1 (c)	75.6 (a)
Abdominal pain (%)	42.7	60.9 (b)	62.6 (b)	68.3 (b)
Vomiting (%)	38.3	52.2 (a)	53.3 (a)	66.7 (c)
Anorexia (%)	31.4	50.5 (b)	51.1 (b)	55 (b)
Pharyngitis (%)	29.1	22.6	23.7	22
Cough (%)	20.6	31.2 (a)	37.6 (b)	29.3
Diarrhea (%)	19.3	44 (c)	44.4 (c)	65.9 (c)
Presyncope/syncope (%)	13.8	27.7 (b)	24.5 (a)	26.2
Rash (%)	9.5	13.2	14.3	9.8
Minor bleeding (%)	8.7	41.5 (c)	37.2 (c)	26.2 (b)

[a] Median values (range).
[b] When compared with patients with uncomplicated dengue fever, (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$, by Mann–Whitney test (age) or chi-square analysis (other categorical data).

the progression of illness to DSS. However, significant differences in clinical presentation of dengue infections exist between children and adults and DHF/DSS is primarily a disease of childhood.[1]

In addition to these classical syndromes, other severe manifestations have been reported.[2,3] These involve mainly the central nervous system, cardiac alterations, and liver damage. Among these severe manifestations, acute hepatitis has been frequently demonstrated in clinical settings[4–8] and on autopsy.[9]

It is believed that early recognition of signs and symptoms of severity is crucial in guiding the management of dengue patients.[10] However, when faced with an apparently uncomplicated case of dengue fever seen during the acute febrile phase, there are still no reliable symptoms to predict the occurrence of a severe outcome.[3]

2. Objectives

The purpose of this study was to explore the possibility that some key symptoms observed during the early febrile phase of dengue fever may help health care providers in identifying patients who are likely to progress to severe disease. For this purpose, we reviewed the records of a cohort of adult dengue patients and examined the statistical relationships between symptoms reported by the patients on admission to an emergency department and the development of severe outcomes.

3. Study design

3.1. Study population

A prospective observational study of acute febrile illnesses was conducted in the emergency department for adults of the University Hospital of Fort-de-France, Martinique, between January 2005 and December 2008. Among the 1353 consecutive febrile patients admitted during the study period, 560 were diagnosed with confirmed dengue infections. The laboratory methods used for the diagnosis of dengue infections have been described elsewhere.[11] The diagnosis was based on positive RT-PCR determinations in 463 patients (82.7%). Serotype 2 was most frequently isolated (64.8% of patients), followed by serotype 4 (12.5%), serotype 3 (3.4%) and serotype 1 (2%). Other patients had only positive anti dengue IgM antibodies ($n=97$, 17.3%). Primary dengue was demonstrated in 128 patients (22.9%) and secondary dengue in 271 patients (48.4%).

3.2. Data collection

Each patient's informed consent was obtained. Data were recorded at the bedside into the computerized medical records system (DxCare, Medasys, Gif sur Yvette, France) by means of a questionnaire implemented for acute febrile illnesses. Clinical forms were identified retrospectively, based on the clinical and biological data recorded at presentation and during the follow-up.[11]

3.3. Covariates included in the analysis

Symptoms included as covariates in the analysis are listed in Table 1. Because the aim of this study was to identify reported symptoms that were associated with a severe course, direct indicators of clinical severity, such as hypotension, signs and symptoms of encephalopathy, severe bleeding, and respiratory failure, were not included in the analysis.

3.4. Definition of severe manifestations

Severe manifestations were defined by the development at any time during the course of illness of any of the following: (1) hypotension (systolic arterial pressure <90 mmHg), (2) signs and symptoms of encephalopathy (alteration of consciousness, convulsions), (3) signs and symptoms of plasma leakage (pleural effusion, ascites, hypoproteinemia and/or hemoconcentration), (4) platelet counts $<20\times10^9$/L, (5) acute hepatitis (aminotransaminases of more than 10-fold the normal upper limits), (6) severe bleeding (bleeding sufficient to warrant consideration for blood transfusion).

3.5. Statistical analysis

Data were analysed with a statistical program (StatView 4.5, Abacus Concepts Inc., Berkeley, CA). First, a bivariate analysis was performed to detect factors significantly associated with severe manifestations. Pearson chi-square tests were used to test for independence in contingency tables. The Mann–Whitney test was used to compare the distribution of continuous variables between two groups. To control for confounding, logistic regression analysis was