Dengue fever in malaria endemic areas

Article *in* Journal of the College of Physicians and Surgeons--Pakistan: JCPSP · June 2006

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ORIGINAL ARTICLE

DENGUE FEVER IN MALARIA ENDEMIC AREAS

Nadir Ali, Asif Nadeem,* Masood Anwar,** Waheed Uz Zaman Tariq,*** and Rashid A. Chotani****

ABSTRACT

Objective: To determine the clinical presentation and frequency of dengue fever in patients presenting with acute febrile illness.

Design: Observational study.

Place and Duration of Study: Combined Military Hospital, Attock in collaboration with Armed Forces Institute of Pathology, Rawalpindi from November 2003 to October 2004.

Patients and Methods: Patients presenting with acute febrile illness were screened for clinical features of dengue fever (DF). Dengue specific IgM was performed in clinically suspected cases. In addition, peripheral smear for malarial parasites and complete blood counts were performed.

Results: Eight hundred patients with fever of less than 2 weeks duration were encountered. Twentytwo (2.75%) presented with the characteristic features of DF. Dengue specific IgM was detected in 11 patients (50%). Nine out of 11 (81.8%) dengue specific IgM positive patients were also positive for malarial parasites on peripheral smear. Out of 11 DF patients, 8 patients (78%) were cured and 3 (28%) died.

Conclusion: Dengue fever should be suspected if patient presents with bleeding manifestations, retrobulbar headache, severe myelgias and/or thrombocytopenia. Malaria and dengue may co-exist; dengue should be excluded in clinically suspected cases by laboratory investigations. Furthermore, surveillance strategies, preventive measures and healthcare workers' education is critical for curtailing this problem.

KEY WORDS: *Dengue fever. Malaria. Pakistan. Acute febrile illness.*

INTRODUCTION

Dengue virus is becoming an increasing public health problem. Over 99% cases of viral hemorrhagic fever reported worldwide are due to dengue hemorrhagic fever (DHF).[1] Dengue fever (DF) is caused by dengue viruses (DENVs), members of the *Flaviviridae* family[2], which contain four closely related serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. All are transmitted to humans by mosquitoes of genus Aedes, principally *A. aegypti*. It has been estimated that 2.5 billion people live in areas which are at risk of epidemic transmission, and over 50 million DENV infections occur globally each year.[3,4] The first epidemic of dengue in Pakistan was reported in 1994.[5,6]

Most of the cases of DENVs are asymptomatic. Among symptomatic cases, the majority suffers from uncomplicated dengue fever but about 3% of the patients develop potentially fatal DHF. DF is characterized by acute febrile illness, headache, retro-orbital pain, nausea, vomiting, rash and myelgias, lasting 3-7 days.[7] In addition to fever and myalgias, three primary diagnostic criteria are the occurrences of vascular permeability defect resulting in hemo-concentration, haemostatic defects including thrombocytopenia, and bleeding manifestations.[8] None of these features are sufficiently specific for accurate clinical diagnosis of DF. Detection of DENV specific IgM, RT-PCR or viral isolation are required to support the diagnosis and to confirm the outbreak.[9]

The classical dengue fever may be confused with a variety of clinical illnesses including malaria.[10] Malaria is endemic in Pakistan and is considered as the most common cause of fever, and in general practice, empirical antimalarial therapy is common. In malaria, the first symptoms are non specific and similar to those of a minor viral illness with malaise, headache, fatigue, abdominal discomfort, and muscle aches, followed by chills and rigors.[11,12] However, it is important to distinguish the two conditions due to unexpected progress of DF to DHF and dengue shock syndrome(DSS). This study was conducted to determine the clinical presentation and frequency of dengue fever in patients presenting with acute febrile illness.

PATIENTS AND METHODS

This observational study was carried out from November 2003 to October 2004. The study was conducted at Combined Military Hospital, Attock, Pakistan. All patients presenting with acute febrile illness were evaluated for clinical features of DF, DHF and DSS. Dengue fever was suspected, if two or more of the following features, in addition to fever, were present: headache, retro-orbital pain, myelgias, arthralgia, scarlatiniform/ maculopapular rash, and hemorrhagic manifestations.[13] Patients with no clinical suspicion of DF were excluded from study. Suspected patients of DF, DHF and DSS were admitted and clinical features were recorded. Graded response of features was determined by treating consultant; 3+ was assigned if the symptom was the chief

Department of Pathology, Combined Military Hospital, Attock.
*Department of Medicine, Armed Forces Intitute of Pathology, Rawalpindi.
**Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
***Department International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.
****Global Infectious Disease Surveillance and Alert System, Johns Hopkins School of Medicine and Public Health, Baltimore, Maryland, USA.

Correspondence: LT Col Nadir Ali, Classified Pathologist, Combined Military Hospital, Malir Cantt., Karachi, Pakistan. E-mail: nmjrm@hotmail.com

Received November 24, 2004; accepted March 27, 2006.

complaint, 2+ was assigned if symptom was one of the complaints but not the chief complaint and 1+ was assigned if the presence of any symptom was noticed on asking the leading question. Two ml of blood in EDTA anticoagulant for blood counts and malarial parasites, and 2 ml blood in plain bottle for detection of dengue specific IgM were collected for the suspected patients. DENV IgM was performed by standardized ELISA method at Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan. Symptomatic treatment was advised for dengue fever patients.[13] In case where malarial parasites were positive, anti-malarial treatment was advised.[12,14] Patients were discharged once asymptomatic. Clinical features and laboratory findings were recorded and descriptive analysis was performed using SPSS 10.0 programmer.

Results

Eight hundred patients with fever were received during the study period at the Department of Medicine, Combined Military Hospital, Attock. Twentytwo (2.75%) patients presented with characteristic features of DF, DHF and DSS. DENV IgM was detected in 11 patients (50%). Malarial parasites were detected in 9 (81.8%) out of 11 DENV IgM positive patients. All DENV IgM positive patients were adults with age range between 17-50 years (mean 27 years), 10 (91%) were male and one was female. All presented with fever, sub lingual temperature ranging from 100°F to 104°F, for a duration of 2-7 days, (mean 4.5 days and median 5 days). Myalgia of 1-3-day duration was complained by 100% patients, and was a chief complaint in 27% (3/11). Headache was a presenting feature in 91% patients, out of which in 36%, it was a chief complaint. Retro-bulbar pain was a presenting feature in 27%, while arthralgia as presenting complaint in 18%. Clinical features of DENV IgM positive cases are summarized in Table I.

Total leukocyte count ranged from 1.1 x10^9 /L to 11.2 x10^9 /L, mean 5.4 x10^9/L (SD of 3.17 x10^9/L). Absolute neutrophil count varied between 0.55 - 6.9 x10^9/L, (mean 3.8 x10^9/L, SD of 2.35 x10^9/L). Low platelet count was the most consistent feature and was detected in 90% patients ranging between 18 to 154 x10^9/L (mean 68 x10^9/L, median 56 x10^9 /L). Prothrombin time (PT), activated partial thromboplasin time (aPTT), fibrinogen degradation products (FDPs), and alanine aminotransferase (ALT) were markedly disturbed in 20% of the patients. Lab findings of DENV positive patients are summarized in Table II.

Eight patients (72%) were cured and 3 patients (28%) died. First patient who died (patient no. 3 Tables I and II), presented with fever, severe body aches, myalgias and headache, was prescribed anti-malarial drugs by a general practitioner in out door, developed severe pain in chest on day 6, and expired next morning. On autopsy *P. falciparum* rings were found in blood and in micro-vasculature. DENV IgM was detected in serum samples collected during autopsy. The second patient who expired was a 50 years old female, (patient no. 5 in Table I and II) who presented with fever, body aches, hemetemesis, and melena. The platelet count was 18 x10^9/L and ALT was 49 u/L. She was given platelet support and symptomatic treatment. On day 14, she developed severe headaches, convulsions, and loss of consciousness and expired the same day. The third patient was a 38 years old male, (patient no. 11 Table I, and II) who presented with fever and convulsions. His blood pressure was 80/40mmHg, platelet count was 18 x10^9/L, ALT was 56 u/L, and cerebro-spinal fluid was clear. Next day he developed gum bleeding, hematuria, melena, and platelet count dropped to 8x10^9/L. Though platelet concentrates were transfused, he expired the next day.

Table I: Clinical features of dengue virus IgM positive patients (n=11).

No	Fever	Myalgias	Arthralgia	Headache	Retro-orbital pain	Bleedings
1	7 days	2+	Nil	2+	nil	Nil
2	2 days	2+	Nil	3+	nil	Nil
3*	7 days	3+	3+	3+	1+	Nil
4	2 days	1+	Nil	2+	nil	Nil
5*	7 days	3+	1+	3+	2+	+
6	3 days	2+	Nil	2+	2+	+
7	7 days	2+	Nil	2+	2+	Nil
8	5 days	1+	Nil	2+	1+	Nil
9	5 days	2+	Nil	2+	nil	Nil
10	3 days	2+	Nil	Nil	1+	Nil
11*	03 days	03	2+	3+	1+	+

*1+: Noticed on leading question; 2+: One of the complaints; 3+: Chief complaint; *Expired.*

Table II: Laboratory findings of dengue virus IgM positive patients (n =11).

TWBC x10^9/L	Neutros x10^9 /L	Platelets x10^9 /L	PT (14 sec)	FDPs (10 ug/L)	aPTT (32 sec)	ALT u/l	Malarial parasites
3.3	2.76	61	15 sec	<10	32 sec	32	*P. vivax*
7.3	5.84	79	14 sec	<10	32 sec	29	*P. vivax*
*	*	*	*	*	*	*	*P.falciparum***
3.5	2.1	45	15 sec	<10	36 sec	35	*P. vivax*
2.3	1.16	18	19 sec	>20	48 sec	49	Not detected
7.0	5.6	35	16 sec	<10	34 sec	42	*P. vivax*
5.6	4.64	56	14 sec	<10	38 sec	40	*P. vivax*
3.8	2.28	154	16 sec	<10	35 sec	38	*P. vivax*
8.9	6.9	98	15 sec	<10	34 sec	28	*P. vivax*
11.2	6.72	116	16 sec	<10	34 sec	30	*P. vivax*
1.1	0.55	18	20 sec	>20	42 sec	56	Not detected

**: Data not available; **: Autopsy finding; TWBC: Total leukocyte count; Neutros: Neutrophils; PT: Prothrombin time; aPTT: activated partial thromboplasin time FDPs: Fibrinogen degradation products ALT: Alanine aminotransferase.*

Three out of 11 patients (28%) died due to DHF as the primary cause of death (patients no. 5 and 11, Table I and II) or DF as associated cause (patient no.3 Table I and II) as suggested by the clinical findings and laboratory data.

Discussion

Due to clinical similarity in two conditions, malaria may easily be confused with DF if the patient is not evaluated carefully.

However, dengue fever may manifest as non-specific febrile illness which can be confused with malaria, especially if peripheral blood smear is positive for malarial parasites. Nine (81.8%) out of 11 dengue patients in this study population had evidence of malarial parasites in peripheral blood smear. Trophozoites of *P. vivax* can be detected in otherwise asymptomatic residents of malaria endemic areas. Such a high number of positive malarial parasites is not likely to be a chance finding. The possibility of extensive mosquito exposure and high co-existence of both conditions can not be excluded. Treating one disease and ignoring the other can lead to unexpected complications of the disease.

Both *P. falciparum* and DSS are associated with shock and subsequent death. In the presence of severe chest and bone pains, associated possibility of DSS cannot be excluded. [5,6,15,16] In two patient, no other associated disorder was recognized. Raised ALT, platelet counts <18 x10^9/L, gastro-intestinal tract bleedings, convulsions suggesting encephalitis, deranged coagulation profile and raised FDPs were associated with more serious and fatal outcome.

Our findings suggest that DHF is an emerging disease in this region. DHF was first reported in Karachi, Pakistan in 1994. [5,6] In 2003, 10 cases of confirmed DF along with 4 deaths were reported in the Haripur (a town 50 kilometers away from the study site). The sera of contacts tested at National Institute of Virology (NIV), South Africa, were positive for DENVs specific IgM . In our opinion, all clinical spectrums including DF, DHF and DSS are present in Pakistan; these simulate malaria in its initial presentation.

The emergence of DHF as a global infectious disease threat is striking in its persistence and magnitude. South East Asia and the Western Pacific region, where DHF was first recognized as a clinical entity, have faced this health problem for almost 50 years. During each decade the number of DHF cases, the number of countries affected and the geographic distribution of DHF have all increased steadily.[3] DF has been reported in Pakistan for the last 10 years. Infection by one serotype renders the patient susceptible to DHF by other serotype because the antibodies formed against pre-existing serotype bind less avidly to the new infecting serotype, and are less effective in neutralizing the virus; in addition, these low avidity antibodies increase in titer in preference to new antibodies with high avidity.[17-20] It can be inferred that the sub-clinical DF, assumingly treated as malaria, is in fact gradually predisposing masses to more severe forms of disease. Failure to recognize this health problem at present stage may lead to larger epidemics of DHF.[21]

It is recommended that health care workers should suspect DF in all cases of febrile illness, and look for specific clinical findings associated with DF, DHF and DSS. Community based education and awareness campaigns should be initiated about the spread, complications and control of disease. Masses and health care workers should know disease as much they are aware of malaria in Pakistan. Breeding places of *Ades aegypti* should be eliminated near human dwellings with personal protection from mosquito bites.

Conclusion

Dengue presents mostly as non-specific febrile illness that resolves with supportive therapy, but the clinical spectrum ranges from mild infection to severe hemorrhage and sudden fatal shock. Dengue fever is not an uncommon entity and the actual number of cases are probably much higher than reported. Presence of malarial parasites in blood leads to diagnostic confusion. DF should be highly suspected if patient presents with bleeding manifestations, retrobulbar headache, severe myelgias and thrombocytopenia. Raised ALT, deranged coagulation profile, raised FDPs, gastrointestinal tract bleedings and involvement of central nervous system are predictors of more serious disease and fatal outcome.

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