ORIGINAL ARTICLE

Clinical Features, Diagnostic Techniques and Management of Dual Dengue and Malaria Infection

Amanullah Abbasi, Nazish Butt, Qurban Hussain Sheikh, Abdul Rabb Bhutto, S.M. Munir and Syed Masroor Ahmed

ABSTRACT

Objective: To find out clinical features, diagnostic techniques and management outcome of patients having dual dengue and malaria infection.

Study Design: A case series.

Place and Duration of Study: Medical Unit-III, Ward- 7, Jinnah Postgraduate Medical Centre, Karachi, from September 2007 to January 2008.

Methodology: Patients presented with fever of less than or equal to 10 days duration, severe body aches, rash and bleeding manifestations were included. Patients with obvious features of other diseases like typhoid, hereditary bleeding diathesis and hematological malignancies and only malarial parasite positive with high grade intermittent fever without rash and myalgia were excluded from the study. Diagnosis of dengue and malaria was based on history, clinical features, laboratory parameters and malarial parasite test by thin and thick films. Serological evaluation was done by dengue IgM and IgG by ELISA test kit.

Patients were divided into three groups. Group A was dengue IgM positive plus MP positive, group B was dengue IgM positive and MP negative and group C was dengue IgM negative and MP negative and were clinically suspected dengue and malaria. The clinical manifestations and laboratory parameters of dual dengue and malaria positive patients were compared with malaria and dengue negative patients.

Results: One hundred and fourteen patients were seen during the study period. Antibody titer (IgM) tested in all patients was found positive in 78 patients (69.64%). Among those 78 patients, 26 (23.21%) were concomitantly positive for malarial parasite (Group A). *Plasmodium vivax* was positive in 25 patients and *falciparum* in one patient. Fifty-two patients (46.42%) were dengue IgM positive and MP negative (Group B). Thirty four (30.35%) patients were MP and dengue IgM negative (Group C) but were strongly suspected for DHF and malaria on clinical and hematological basis. The hemoglobin of 34.61% of patients of group A, 5.76% of group B and 14.7% of group C were low, hematocrit level was also low in group A (92.3%), group B (15.38%) and group C (70.58%) patients. The platelet count was markedly low in 84.61% of patients of group A, 57.69% of group B and 94.11% of group C. Leukopenia was found in 34.61% of patients of group A, 78.84% in group B and 29.411% in group C. The liver function tests were deranged in all groups.

Conclusion: The frequency of dual dengue and malaria infection was 23.21%. The serology of the dengue and malaria showed negative results in 30.35%. The diagnosis of dual infections could be made on the basis of history, clinical examination supported by hematological results. It is recommended that all the patients suspected for dual infections should be treated concomitantly for dengue and malaria in malaria endemic areas.

Key words: *Dengue. Malaria. Dual infection. Fever.*

INTRODUCTION

Dengue fever and malaria are the most common arthropod borne diseases of mankind and emerged as a global public health problem. Malaria is a protozoan disease transmitted by the bite of infected Anopheles mosquitoes.[1] Symptoms of malaria are non-specific; there may be a prodromal period of tiredness and aching followed by fever, which may last from 6 to 10 hours.[2] Dengue is a viral infection and is transmitted by Aedes aegypti, which is found worldwide between latitudes 35° N and 35° S.[3,4]

Ward No. 7, Jinnah Postgraduate Medical Centre, Karachi.

***Correspondence:** Dr. Amanullah Abbasi, Flat No. 8, Category-IV, Block-A, Doctors' Colony, Jinnah Postgraduate Medical Centre, Karachi.*
E-mail: draman_ullah2000@yahoo.com

Received March 6, 2008; accepted October 23, 2008.

In Pakistan, the first confirmed outbreak of Dengue Haemorrhagic Fever (DHF) was reported in 1994; the serotype reported was DENV-2.[5] During the year 2005-2006, however, there was an unprece-dented increase in epidemic DHF activity in the country, with a large number of cases being reported from Karachi.[6]

DF can occur simultaneously with many viruses and bacteria.[7,8] It is found in the geographical areas similar to malaria with increased incidence during the rainy and post-rainy season.[9-11] The acquisition of both vector borne infections is concurrently possible.[12]

In a recently conducted study in Pakistan, 9 out of 11 patients with dengue specific IgM were also found positive for malarial parasites on the peripheral smear.[13] Dengue virus causes a broad spectrum of illness ranging from mild undifferentiated fever to classical dengue fever, and Dengue Shock Syndrome (DSS).[14]

Although fever, retrobulbar headache, rash, myalgia and vomiting are the most frequent symptoms, it should be suspected if a patient meets the three diagnostic criterias of thrombocytopenia, hemoconcentration and elevated ALT and AST.[12-18]

The objective of this study was to find out clinical features, diagnostic techniques and management outcome of patients having dual dengue and malaria infection.

METHODOLOGY

A descriptive case series study was conducted from September 2007 to January 2008. Specific beds were assigned in Ward 7, Jinnah Postgraduate Medical Centre, Karachi for the studied group.

Patients presenting with fever of less than or equal to 10 days duration, severe body aches, rash and bleeding manifestations were included. Patients with obvious features of other diseases like typhoid, hereditary bleeding diathesis and hematological malignancies and the malarial parasite positive with high-grade intermittent fever without rash and myalgia were excluded from the study. Demographic data such as age, gender and residence, and epidemiological data such as exposure to mosquito bites were recorded. Detailed clinical history and examination were carried out and recorded in a performed proforma.

Complete blood count with peripheral film, malarial parasite thick and thin film stained with Giemsa stain, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), liver function test (LFT), dengue viral specific immunoglobulin detection (IgG, IgM), typhoid test and blood grouping and cross match.

Patients were divided into three groups. Group A was dengue IgM positive plus MP positive and combined clinical features. They were given parenteral fluid therapy according to WHO guidelines, paracetamol, antimalarial therapy as quinine sulfate 600 mg thrice plus doxycycline 100 mg daily for 7 days in cases of *Plasmodium falciparum*, Coartem (artemether 20 mg, lumefantrine 120 mg) four tablets twice daily for 3 days, after which primaquine 0.6 mg/kg was given once a day for 14 days in cases of *Plasmodium vivax*; and platelet concentrates (platelet count $<20,000x10^9$/L), colloidal solutions and blood support in cases of circulatory failure. Group B was dengue IgM positive and MP negative with fever, body rash, myalgia and bleeding manifestations. They were given parenteral fluid therapy according to WHO guidelines, paracetamol, and platelet concentrates (in patients with platelet count of $<20,000x10^9$/L), colloidal solutions and blood support in cases of circulatory failure. Group C was dengue IgM negative and MP negative but had combined clinical features (intermittent prolonged fever, rash, myalgia, bleeding manifestation and anemia) of dengue and malaria. They were given antimalarial and parenteral fluid therapy, paracetamol, and platelet concentrates colloidal solutions and blood support in cases of circulatory failure.

The patients were discharged after 5-7 days when there was absence of fever for 24 hours, platelet count $>50,000^x10^9$/L, good urine output and improvement in symptoms of vomiting, anorexia and abdominal pain.

Data were processed and analyzed with SPSS for Windows software version 12.0.

RESULTS

During the study period, 114 patients met the inclusion criteria. Two patients were excluded from the study, one patient suffered from acute leukemia and other from malaria. Eighty two patients were male and 30 were female. The age varied from 13 years to 70 years with the mean of 41.5 years. The symptoms and clinical findings are stated in the Table I. Laboratory findings of probable and proven dual dengue and malaria patients are summarized in Table II. Antibody titer (IgM) tested in all patients was found positive in 78 patients (69.64%). Among those 78 patients, 26 (23.21%) were concomitantly positive for malarial parasite (Group A). *Plasmodium vivax* was positive in 25 patients and *falciparum* in one patient. Fifty two patients (46.42%) were dengue IgM positive and MP negative (Group B). Thirty four (30.35%) patients were MP and dengue IgM negative (Group C) but were strongly suspected for DHF and malaria on clinical basis. The hemoglobin level of 34.61% of patients of group A, 5.76% of group B and 14.7% of group C were low. The hematocrit (Hct) level was also low in group A (92.3%), B (15.38%) and C (70.588%) patients. The platelet count was markedly low in 84.61% of patients of group A, 57.69% of group B and 94.11% of group C. The leukopenia was found in 34.61% of patients of group A, 78.84% in group B and 29.411% in group C. The liver function tests were deranged in all groups.

Table I: Common symptoms and clinical findings (n=112).

Fever	112	100%
Conjunctival injection	100	89.28%
Morbiliform rash	91	81.25%
Vomiting	88	78.57%
Anorexia	78	69.64%
Abdominal pain	73	65.17%
Bodyache	71	63.39%
Hepatomegaly	62	55.35%
Bleeding manifestations	40	35.71%
Spleenomegaly	18	16.07%
Lymphadenopathy	17	15.17%
Pleural effusion	11	9.82%
Ascites	8	7.14%

Patients with bleeding manifestation and platelet count $< 20,000x10^9$ without bleeding was transfused with a

Table II: Hematological and biochemical findings (n=112).

Investigation	Range	Remarks	Group A (n=26)	Group B (n=52)	Group C (n=34)
Hemoglobin (gm/dl)	3.6-16.6	>10	17	49	29
		7-10	6	3	4
		<7	3	0	1
Hematocrit (%)	10-49	<20	4	2	6
		20-45	20	6	18
		>45	2	44	10
Platelet count/mm^3	5000-100,000	50,000-10,0000	4	22	2
		20,000-50,000	16	28	29
		<20,000	6	2	3
Leukocyte count 10^3/L	1.1-11.2	>4.6	17	11	24
		1.6-4.5	7	32	7
		<1.5	2	9	3
ALT (U/L)	31-352	41-120	18	26	21
		>120	7	24	11
AST (U/L)	40-823	<40	2	2	1
		41-120	11	21	15
		>120	13	29	18
Gamma-GT (U/L)	16-248	<60	1	3	1
		61-120	19	38	22
		>120	6	11	11

mean 6 units of 50 ml of platelets. Patients who had Hct of < 20% were transfused with 2 units of 200 ml red cells (4 patients). The symptoms were resolved in 4 days, except fever, which was prolonged in patients with dual infection. The average stay in the hospital was 6 days.

DISCUSSION

The emergence of DHF is becoming a public health problem in Karachi. The expansion of this *flavivirus* infection is linked to resurgence of the mosquito vector *Aedes aegypti*, population growth, uncontrolled urbanization and overcrowding without appropriate water and waste management, and global spread of dengue via travel and trade.[29] Pakistan is located on the endemic belt of malaria, and the incidence is one case per thousand population.[20] Dual infections are not uncommon in malaria.[21] It would be expected that coexisting malaria and dengue infection would be common in areas where both illnesses are endemic. Dual infections with two infectious agents can result in an illness having overlapping symptoms, resulting in a situation where both diagnosis and treatment of a patient may become difficult for a physician. The patients with combined infection had prolonged fever of more than 7 days, myalgias, bleeding manifestations, rash and anemia. Patients with dengue infection had high-grade continuous fever lasting for 3-7 days duration, myalgia, rash, bleeding manifestation, hepatomegaly, raised hematocrit, thrombocytopenia, elevated ALT and AST.[18,22]

Similarly, malaria produces fever, headache, malaise, abdominal discomfort; vomiting and other flu like symptoms, but rash is not the characteristic feature of malaria.[1] Complicated *falciparum* malaria can produce altered level of consciousness, renal failure, hypotensive shock, pulmonary edema, abdominal pain with diarrhea, hepatosplenomegaly, spontaneous bleeding and coagu-lopathy, hyper-pyrexia and unarousable coma.[23]

Differentiating malaria from dengue, based on purely clinical grounds is difficult. Compared with those with malaria, patients with dengue are more likely to develop abrupt onset of fever, with severe headache, myalgias and arthralgias (severe pain gives it the name of break bone fever), and rashes.[24]

The hematocrit and hemoglobin level was low in group A and C patients as compared to group B. The platelet count was markedly low in both groups A and C as compared to group B. Hematological abnormalities have been observed in patients with malaria, anemia and thrombocytopenia being the most common, but hemoconcentration may indicate dengue.[25,26] The leukocyte count was markedly low in group B as compared to group A and C. Compared with other febrile illnesses, dengue fever is 18 times more likely if fever and leukopenia are present, 71 times more likely if fever and rash are present, and 230 times more likely if fever, rash, and leukopenia are present.[16]

Severe thrombocytopenia is common in isolated *falciparum*, mixed *falciparum/vivax* malaria and in co-infection with dengue, but is very rare in isolated *P. vivax* infection.[26] In this study, thrombocytopenia was found in all patients, but markedly low in patients with dual dengue and malaria infection. The liver function tests were deranged in all groups. Although, liver is not the target organ of dengue virus, several pathological findings including fatty change, centrilobular necrosis and monocyte infiltration in the portal tract is reported.[27,28] In the patients only positive for dengue IgM, and those not positive for dengue or malaria, one can not rule out the presence of dual infection. The IgM production varies considerably among the patients.

Some patients will have IgM detectable by the 2nd to the 4th day after the beginning of the symptoms, while others do not develop detectable IgM until the 8th day after the disease onset. Some anti-dengue IgM false negative reactions are observed in secondary infection. A small percentage of patients have secondary infection with no detectable IgM antibodies.[29,30] Similarly, the diagnosis of malaria by thick and thin films for malarial parasites has an operator dependent sensitivity of 80-90%.[31] In experienced hands, microscopy can detect lower parasite counts and it is still considered the Gold standard test.[32]

In the light of above results, prolonged fever with normal to low hematocrit and marked thrombocytopenia indicate dual infection. The clinical signs, symptoms and laboratory investigations of dengue IgM and MP positive compared with dengue IgM and MP negative patients were similar. The outcomes of patients treated for dual infection were good. Cases reported from France, India and Pakistan have shown that delayed diagnosis resulted in fatal complications.[9,13,33] Therefore, treatment should be instituted to cover the dual infection.

CONCLUSION

The frequency of dual dengue and malaria infection was 23.21%. The serology of the dengue and malaria showed negative results in 30.35%. The diagnosis of dual infections should be made on the basis of history, clinical examination supported by hematological results. Therefore, it is recommended that all the patients suspected for dual infections should be treated concomitantly for dengue and malaria in malaria endemic areas.

REFERENCES

1. White NJ, Breman JG. Malaria and babesiosis: diseases caused by red cell parasites. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, (edi). Harrison's principles of internal medicine. 16th ed. New York: *McGraw- Hill*; 2005:p.1218-32.
2. Mohapatra MK. The natural history of complicated *falciparum* malaria: a prospective study. *J Assoc Physicians India* 2006; **54**:848-53.
3. Gibbons RV, Vaughan DW. Dengue: an escalating problem. *BMJ* 2002; **324**:1563-6.
4. Lanciotti RS, Calisher CH, Chang GJ, S. AC, V. AV. Rapid detection and typing of dengue viruses from clinical samples by using reverse transcriptase-polymerase chain reaction. *J Clin Microbiol* 1992; **30**: 545-51.
5. Chan YC, Salahuddin NI, Khan J, Tan HC, Seah CL. Dengue hemorrhagic fever outbreak in Karachi, Pakistan, 1994. *Trans R Soc Trop Med Hyg* 1995; **89**: 619-20.
6. Khan E, Siddiqui J, Shakoor S, Mehraj V, Jamil B, Hasan R. Dengue outbreak in Karachi, Pakistan, 2006: experience at a tertiary care centre. *Trans R Soc Trop Med Hyg* 2007; **101**:1114-9.
7. Sudjana P, Jusuf H. Concurrent dengue hemorrhagic fever and typhoid fever infection in adult: case report. *Southeast Asian J Trop Med Public Health* 1998; **29**:370-2.
8. Bhalla A, Sharma N, Sharma A, Suri V. Concurrent infection with dengue and malaria [letter]. *Indian J Med Sci* 2006; **60**:330-1.
9. Charrel RN, Brouqui P, Foucault C, de Lamballerie X. Concurrent dengue and malaria [letter]. *Emerg Infect Dis* 2005; **11**:1153-4.
10. Guzman MG, Kouri G. Dengue: an update. *Lancet Infect Dis* 2002; **2**:33-42.
11. Indaratna K, Hutubessy R, Chupraphawan S, Sukapurana C, Tao J, Chunsutthiwat S, *et al.* Application of geographical information systems to co-analysis of disease and economic resources: dengue and malaria in Thailand. *Southeast Asian J Trop Med Public Health* 1998; **29**:667-8.
12. Ansari JK, Siddiq M, Hussain T, Baig I, Tariq WZ. Outbreak of dengue hemorrhagic fever in Karachi. *Pak Armed Forces Med J* 2001; **5**:94-8.
13. Ali N, Nadeem A, Anwar M, Tariq WZ, Chotani RA.. Dengue fever in malaria endemic areas. *J Coll Physicians Surg Pak* 2006; **16**:340-2.
14. Rong-Fuchen, Kuender DY. Different Clinical and laboratory manifestations between dengue hemorrhagic fever and dengue fever with bleeding tendency. *Trans R Soc Trop Med Hyg* 2007; **101**:1106-13.
15. Ayyub M, Khazindar AM, Lubbad EL, Barlas S, Alfi AY, Ukayli SA. Characteristics of dengue fever in a large public hospital, Jeddah, Saudi Arabia. *J Ayub Med Coll Abottabad* 2006; **18**:9-13.
16. Sung V, O'Brien DP, Matchett E, Brown GV, Torresi J. Dengue fever in travelers returning from South-east Asia. *J Travel Med* 2003; **10**:208-13.
17. Akram DS, Igrashi A. Dengue virus infection among children with undifferentiated fever in Karachi. *Infect Dis J* 2000; **9**:10-4.
18. Butt N, Abbassi A, Munir SM, Ahmad M, Sheikh QH. Hematological and biochemical indicators for the early diagnosis of dengue viral infection. *J Coll Physicians Surg Pak* 2008; **18**:282-5.
19. Lifson AR. Mosquitoes, models and dengue. *Lancet* 1996; **347**:1027-33.
20. Memon AR, Afsar S. Thrombocytopenia in hospitalized malaria patients. *Pak J Med Sci* 2006; **22**:141-3.
21. Kaushik RM, Varma A, Kaushik R, Gaur KKBS. Concurrent dengue and malaria due to *Plasmodium falciparum* and *P. vivax*. *Trans R Soc Trop Med Hyg* 2007; **101**:1048-50.
22. Saxena AK. Dengue in travelers. *N Engl J Med* 2005; **353**:2511-3.
23. Baheti R, Laddha P, Gehlot RS. Liver involvement in *falciparum* malaria–a histopathological analysis. *JIACM* 2003; **4**:34-8.
24. Janis EB. Evaluation of fever in the international traveler. Unwanted 'souvenir' can have many causes. *Postgrad Med* 2004; **116**:13-29.
25. Richard MW, Behrens RH. Hematological changes in acute imported *Plasmodium* malaria. *Am J Trop Med Hyg* 1998; **59**:859.
26. Katira B, Shah I. Thrombocytopenia in *Plasmodium vivax* infected children. *J Vect Borne Dis* 2006; **43**:147-9.
27. Hurre MR, Lan NT, Marianneau P, Hue NB, Khan H, Hung NT, *et al.* Liver histopathology and biological correlates in five cases of fatal dengue fever in Vietnamese children. *Virchows Arch* 2001; **438**:107.

28. Luiz JDS, RMRN, Leandro CS, Carlos ECS, Bruno FR. The impact of dengue on liver function as evaluated by amino-transferase levels. *Braz J Inf Dis* 2007; **11**:407-10.

29. De Paula SOD, Fonceca BA. Dengue: a review of the laboratory tests, a clinician must know to achieve a correct diagnosis. *Braz J Inf Dis* 2004; **8**:390 -8.

30. Guzman MG, Kouri G. Dengue diagnosis, advances and challenges. *Int J Infect Dis* 2004; **8**:69-80.

31. Craig MH, Sharp BL. Comparative evaluation of four techniques for the diagnosis of *Plasmodium falciparum* infections. *Trans R Soc Trop Med Hyg* 1997; **91**:279-82.

32. Hanscheid T. Diagnosis of malaria: a review of alternatives to conventional microscopy. *Clin Lab Haematol* 1999; **21**:235-45.

33. Ward DI. A case of fatal *Plasmodium falciparum* malaria complicated by acute dengue fever in East Timor. *Am J Trop Med Hyg* 2006; **75**:182-5.