

## CONCURRENT DENGUE INFECTION AND ENTERIC FEVER. A CASE SERIES

Parwati Setiono Basuki

### ABSTRACT

*Fever is often the symptom that prompts patients to seek medical care. Classic typhoid fever begins with a remittent fever pattern that becomes sustained over the first few days of illness. Dengue virus infection may be asymptomatic or may lead to undifferentiated febrile illness, dengue fever, or dengue hemorrhagic fever depending largely on age and immunological conditions. Four cases of concurrent enteric fever and dengue virus infection are reported. Among these cases three had prolonged fever around 9-13 days, and were therefore suspected for typhoid fever. Blood cultures yielded *S. typhi* in 3 cases and *S. paratyphi* in one. Since patients in this series served as controls in a study of dengue infection, a serologic assay (dengue rapid test) was assigned, by which anti-dengue IgM were detected in all cases, along with a positive HI test in one case, compatible with a primary infection. Clinical manifestations included prolonged fever in 3 cases, along with abdominal pain, anorexia and liver enlargement. In all but one case there was evidence of nausea, vomiting, headache, and two children showed change in mental status. Obviously there were no signs of bleeding, nor was there evidence of plasma leakage. Two cases were afebrile when discharged, while in the other two, low-grade fever persisted when discharged on request. Taking into consideration that the predominating anti-dengue immunoglobulin was of the IgM isotype, dengue virus infection was presumed to be recent primary infection. Dealing with prolonged fever should always alert the physician of other serious infections, which may be potentially fatal if not promptly recognized and treated. From the epidemiology point of view, family members often manage dengue fever symptomatically, and consequently the diagnosis of dengue infection will be overlooked, remaining unreported.*

**Keywords:** dengue infection, enteric fever, prolonged fever, concurrent infection

### INTRODUCTION

Fever is often the symptom that prompts patients to seek medical care. A thorough fever history includes information about the date of onset, the fever pattern, and temperature range. The number of possible pathogens that cause fever can seem overwhelming to the clinician, and a careful approach to these patients will permit the physician to gather information that can lead to the diagnosis.

Several key symptoms may help generate a differential diagnosis. Severe myalgia and retro-orbital pain are frequently seen in dengue fever. Chills can be indicative of many febrile illnesses, but are particularly prominent in malaria, dengue, and bacterial infections. Spontaneous bleeding or bruising may suggest a hemorrhagic viral infection, such as dengue hemorrhagic fever. Diarrhea, in combination with fever, is typically caused by bacterial pathogens such as *Escherichia*, *Campylobacter*, *Salmonella* and *Shigella* species. These organisms may even cause septicemia and produce high fevers, both before and during the onset of diarrhea. Diarrhea is a complaint in 30-50% of patients with typhoid fever (Suh 2000).

Dengue infection and typhoid fever are endemic diseases in Indonesia; signs and symptoms may overlap, especially during the first few days of illness and are indistinguishable from many tropical infectious diseases (Suh 2000).

This paper reports four cases of enteric fever (typhoid and paratyphoid fever) which revealed positive for IgM anti dengue. The arbovirus infection was initially not included in the differential diagnosis because most of the patients were admitted with a suspicion of prolonged fever. However, because these cases served as controls in a study on dengue infection a Dengue Rapid Test was performed.

### CASE SERIES

This series consisted of patients who served as controls in a study of dengue infection and were therefore tested for the presence of IgM and IgG antibodies against dengue.

#### Case 1:

E, a nine and a half year-old girl was admitted with fever lasting for 9 days. Associating signs and symptoms included sore throat, headache, and loss of appetite, abdominal pain, nausea, vomiting, and constipation. There were no signs of bleeding. Physical

---

*Infection and Tropical Pediatrics,  
Department of Child Health  
Airlangga University School of Medicine,  
Dr Soetomo Teaching Hospital, Surabaya*

examinations at admission revealed an alert child with a body weight of 24 Kg, blood pressure of 100/70 mm Hg, pulse rate 128/min, respiration rate 30/min, and a temperature of 38 °C. Tourniquet test was not performed. The pharynx was injected; heart and lungs were normal. The abdomen was flat, along with normal bowel sounds; the liver was palpable 2 cm below the costal margin. There was no evidence of pleural effusion or ascites. Initial diagnosis at admission was acute pharyngitis, and Amoxicillin was started. However, considering the prolonged fever, typhoid fever was considered as a differential diagnosis. Laboratory examinations revealed hemoglobin 12 g/dl (at admission), and 12.6 g/dl (repeated on the third day of admission), hematocrit 33.7% (at admission), and 35.3% (repeated on the third day of admission), leukocyte 8900/cmm, differential count eosinophil 1, basophile 0, stab 1, segment neutrophil 39, lymphocyte 59, monocyte 0, thrombocyte  $152 \times 10^9/\mu\text{L}$ . The ALT was 10 IU, AST 15 IU, and the renal function test was within normal limits. Widal test revealed a titer of 1/400 and 1/400 against O and H antigens for *S. typhi* respectively. Blood culture yielded *Salmonella typhi*. Serological assay (Dengue Rapid Test) resulted in the presence of IgM antibodies against dengue virus. Hemagglutination Inhibition test revealed negative. Accordingly the diagnosis of typhoid fever as well as dengue infection was established. On follow up the patient did not experience any complication, fever gradually decreased to normal on the seventh day of hospitalization.

#### Case 2:

H, a nine year-old boy was admitted with fever lasting for 10 days, increasing step-ladder wise day by day along with chills and delirium. Associating signs and symptoms included headache, loss of appetite, abdominal pain, and constipation. There were no signs of bleeding. Physical examinations at admission revealed an alert child with a body weight of 19 Kg, blood pressure of 110/70 mm Hg, pulse rate 120/min, respiration rate 24/min, and a temperature of 39.3 °C. Tourniquet test was not performed. The pharynx was injected; heart and lungs were normal. The abdomen was flat, along with normal bowel sound; the liver was palpable 3 cm below the costal margin. There was no evidence of pleural effusion or ascites. Initial diagnosis at admission was typhoid fever, and Amoxicillin was started. Laboratory examinations revealed hemoglobin 12.4 g/dl (at admission), and 10.5 g/dl (repeated on the third day of admission), hematocrit 35% (at admission), and 32% (repeated on the third day of admission), leukocyte 10.100/cmm, differential count eosinophil 0, basophile 0, stab 0, segment neutrophil 55, lymphocyte 45, monocyte 0, thrombocyte  $420 \times 10^9/\mu\text{L}$ . The ALT

was 10 IU, AST 18 IU, and the renal function test was within normal limits. Widal test revealed a titer of 1/400 and 1/800 against O and H antigens for *S. typhi* respectively. Blood culture yielded *Salmonella typhi*. Serological assay (Dengue Rapid Test) resulted in the presence of IgM antibodies against dengue virus. Hemagglutination-Inhibition test revealed negative. Accordingly the diagnosis of typhoid fever and dengue infection were established. On follow up the patient did not experience any complication, except that the fever persisted when he went home on request on the eighth day of hospitalization.

#### Case 3:

M, an eleven year-old boy was admitted with fever lasting for 4 days. Associating signs and symptoms included delirium, cough, and headache, loss of appetite, abdominal pain, epigastric pain, nausea, vomiting, and diarrhea. There were no signs of bleeding. Physical examination at admission revealed a lethargic child with a body weight of 22 Kg, blood pressure of 100/70 mm Hg, pulse rate 120/min, respiration rate 24/min, and a temperature of 39.6 °C. Tourniquet test was not performed. The pharynx was injected, there was enlargement of the tonsils; heart and lungs were normal. The abdomen was flat, along with meteorism; the liver was palpable 1 cm below the costal margin. There was no evidence of pleural effusion or ascites. Initial diagnosis at admission was typhoid fever, and malnutrition, and Amoxicillin was started. Laboratory examinations revealed hemoglobin 10.5 g/dl (at admission), and 10.4 g/dl (repeated on the third day of admission), hematocrit 36% (at admission), and 35% (repeated on the third day of admission), leukocyte 8600/cmm, differential count eosinophil 0, basophile 0, stab 2, segment neutrophil 24, lymphocyte 74, monocyte 0, thrombocyte  $235 \times 10^9/\mu\text{L}$ . The ALT was 45 IU, AST 58 IU, and the renal function test was within normal limits. Widal test revealed a titer of 1/400 and 1/100 against O antigens for *S. paratyphi* A and *S. paratyphi* B respectively. Blood culture yielded *Salmonella paratyphi* A. Serological assay (Dengue Rapid Test) resulted in the presence of IgM antibodies against dengue virus. Hemagglutination Inhibition test revealed negative. Accordingly the diagnosis of typhoid fever and dengue infection were established. On follow up the patient did not experience any complication, he gradually improved and fever decreased to low-grade fever on the fifth day of hospitalization. The patient was discharged on request on the thirteenth day of hospitalization.

**Case 4:**

S, a six and a half year-old girl was admitted with fever lasting for 13 days. Associating signs and symptoms included loss of appetite, abdominal pain, nausea, vomiting, and diarrhea. There were no signs of bleeding. Physical examinations at admission revealed an apathetic child with a body weight of 11 Kg, blood pressure of 95/60 mm Hg, pulse rate 140/min, respiration rate 36/min, and a temperature of 39 °C. Tourniquet test was not performed. The lips were dry, a coated tongue was evident, heart and lungs were normal. The abdomen was meteoristic, along with a normal bowel sound; the liver was palpable 3 cm below the costal margin. There was no evidence of pleural effusion or ascites. Initial diagnosis at admission was typhoid fever and malnutrition, and Amoxicillin was started. Laboratory examinations revealed hemoglobin 9.9 g/dl (at admission), and 8.8 g/dl (repeated on the third day of admission), hematocrit 30% (at admission), and 25% (repeated on the third day of admission), leukocyte 7400/cmm, differential count eosinophil 0, basophil 0, stab 0, segment neutrophil 57, lymphocyte 43, monocyte 0, thrombocyte  $250 \times 10^9/\mu\text{L}$ . The ALT

was 92 IU, AST 100 IU, serum albumin 3.5 g/dl, serum globulin 3.3 g/dl, Sodium 128 mMol/L, Potassium 2.7 mMol/L, and the renal function test was within normal limits. Widal test revealed a titer of 1/800 and 1/800 against O and H antigens for *S. typhi* respectively. Blood culture yielded *Salmonella typhi*. Serological assay (Dengue Rapid Test) resulted in the presence of IgM antibodies against dengue virus. Hemagglutination-Inhibition test revealed positive concluding a primary response. Accordingly the diagnosis of typhoid fever as well as dengue infection was established. On follow up the patient gradually improved, on the fifth day of admission she started to ask for food. Despite having low-grade fever she was discharged on request on the ninth day of hospitalization.

**DISCUSSION**

All patients were bacteriological proven for enteric fever, 3 patients with typhoid fever and one with paratyphoid fever. The Widal test ranged from 1/200 to 1/800 against O and H antigens for *Salmonella*. Clinical figures are shown below.

Table 1. Clinical and laboratory findings of patients reported in the case series

Clinical/laboratory findings	Case 1	Case 2	Case 3	Case 4
Sex	Female	Male	Male	Female
Age (years)	9.5	9	11	6
Body Weight	24	19	22	11
Fever-day	9	10	4	13
At admission				
Loss of appetite	+	+	+	+
Sore throat	+	-	-	-
Abdominal pain	+	+	+	+
Nausea	+	-	+	+
Vomiting	+	-	+	+
Constipation	+	+		
Diarrhea	-	-	+	+
Headache	+	+	+	-
Cough	-	-	+	-
Consciousness	Alert	Alert	Lethargic	Apathetic
Blood pressure	100/70	110/70	100/70	95/60
Liver enlargement	2 cm	3 cm	1 cm	3 cm
Meteorism	-	-	+	+
Signs of bleeding	-	-	-	-
Signs of CNS	-	Delirium	Delirium	-
Fever-day of defervescence	7	Inconclusive*	5	Inconclusive*
Hemoglobin-at admission-	12 g/dl	12.4 g/dl	10.5 g/dl	9.9 g/dl
Hemoglobin-on follow up-	12.6 g/dl	10.5 g/dl	10.4 g/dl	8.8 g/dl
Hematocrit-at admission-	33.7 %	35 %	36 %	30 %
Hematocrit-on follow up-	35.3 %	32 %	35 %	25 %
Leukocytes	8900/cmm	10.100/cmm	8600/cmm	7400/cmm
Thrombocytes	152 x 10 <sup>9</sup> /μL	420 x 10 <sup>9</sup> /μL	235 x 10 <sup>9</sup> /μL	250 x 10 <sup>9</sup> /μL
Aneosinophylia	-	+	-	-
ALT/AST	10 IU / 15 IU	10 IU/18 IU	45 IU/ 58 IU	92 IU/ 100 IU
Serum electrolytes	ND	ND	ND	Sodium 128 mMol/L, Potassium 2.7 mMol/L
HAI test	Neg	Neg	Neg	Posden-primary
Dengue Rapid Test	IgM anti dengue	IgM anti dengue	IgM anti dengue	IgM anti dengue
Widal test	1/400 O, 1/400 H	1/400 O, 1/800 H	1/400 paraty A, 1/100 paraty B	1/800 O, 1/800 H
Blood culture	<i>S. typhi</i>	<i>S. typhi</i>	<i>S. paratyphi</i>	<i>S. typhi</i>

\* Patients were discharged on request

Except for case 3, patients experienced fever for more than one week, suggesting a prolonged fever. Consequently prompt initial antibiotic therapy was considered appropriate since all the cases presented with gastro-intestinal problems and two even had CNS

disturbance (case 3 and 4). These were all in accordance with typhoid fever where the management should follow five steps; namely, (1) making a presumptive clinical diagnosis based on history, physical examination and results of laboratory tests; (2) culturing

relevant clinical specimens to confirm the diagnosis; (3) prompt initiation of appropriate antibiotic therapy; (4) careful monitoring of the patient to detect complications; (5) epidemiologic investigation to identify other cases among contacts and to detect chronic carriers who may have been responsible for transmission (Stephens 2002)

Bacteriologic confirmation was made by isolation of *S. typhi* in 3 cases and *S. paratyphi* A in one, from culture of the blood. Serologic tests for *Salmonella agglutinins* (Widal test) also provided suggestive evidence of *S. typhi* and *S. paratyphi* infection. However, these tests are of little value in older children and adults and continue to be plagued with controversies involving the quality of the antigens used and interpretation of the result particularly in endemic areas (Stephens 2002, Olopoenia 2000)

In these case series clinical and laboratory evidence were not conclusive for either enteric fever or dengue infection. Overlapping signs and symptoms of these infections included fever, loss of appetite, abdominal pain, nausea, vomiting, headache, and liver involvement.

Because three of the patients came with fever more than 7 days, it can be accepted that in the differential diagnosis one would not consider dengue infection as the first priority and this will, from the epidemiologic point of view, lead to under reporting, as cases of dengue infection will be overlooked.

Fever lasted for 16 days and 9 days for case 1 and case 3 respectively, while for case 2 and 4 it was not possible to conclude when the fever subsided, because they were discharged on request and lost to follow-up. (See Figure 1)

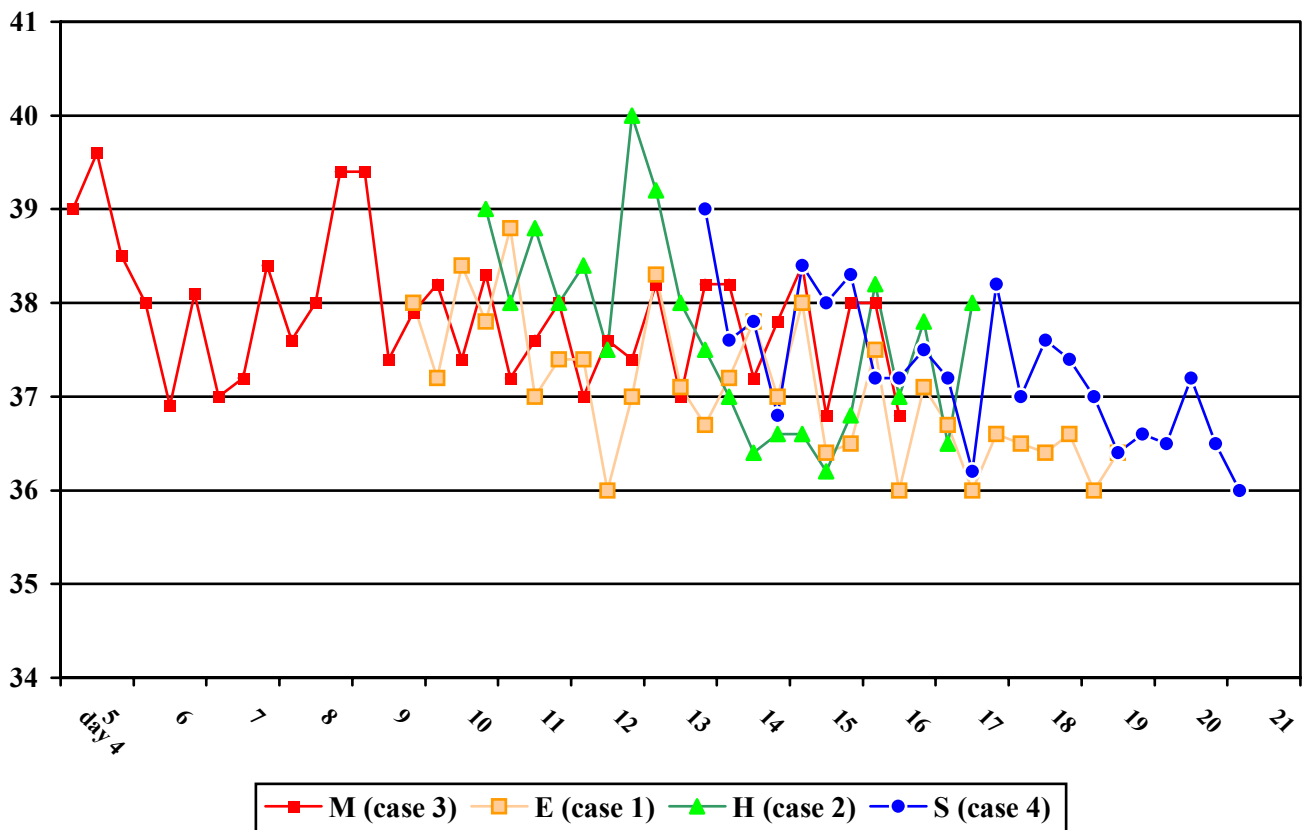


Fig.1 Fever pattern in 4 cases with enteric fever and anti-dengue IgM antibodies

Detectable levels of anti-dengue antibodies appear after several days of fever. Two patterns of immune response are distinguished: primary and secondary (anamnestic). Persons never previously infected with a flavivirus, nor immunized with a flavivirus vaccine, mount a primary antibody response when infected with a dengue virus. The dominant immunoglobulin isotype is IgM. Anti-dengue IgM detectable by IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) appears in half of the patients with a primary infection while they are still febrile; in the other half, it appears within 2-3 days of defervescence. Once detectable, IgM levels rise quickly and appear to peak about 2 weeks after the onset of symptoms, then they decline to undetectable levels over 2-3 months. Anti-dengue antibodies inhibit the haemagglutination of gander red blood cells by dengue virus; haemagglutination-inhibiting antibodies appear simultaneously with the detection of IgM by immuno-assay. Anti-dengue IgG appears shortly afterwards.

Individuals with immunity to previous flavivirus infection or immunization mount a secondary (anamnestic) antibody response when infected with dengue virus. In secondary flavivirus infection, which accounts for most cases of DHF, the dominant immunoglobulin type is IgG. Anti-dengue IgM appears in most instances, and while the kinetics of IgM production are similar to those observed in primary infections, the levels of IgM are dramatically lower. In contrast to primary infection, secondary infection with dengue virus result in the appearance of high levels of anti-dengue IgG before, or simultaneously with, the IgM response. Once detected, IgG levels increased quickly, peak about 2 weeks after the onset of symptoms and then decline slowly over 3-6 months. Anti-dengue IgM levels also peak at about 2 weeks, begin to wane thereafter and are detectable in about 30% of patients 2 months after the onset of symptoms (Anonymous 1997)

Anti-dengue IgM was detected in all 4 cases, conclusive for a recent dengue infection. However it is not easy to exactly determine when the patient experienced the disease. Taking into consideration that the immunoglobulin detected was solely the IgM isotype, dengue infection in this case series should have been a primary infection. Immunoglobulin-M antibodies wane relatively rapidly, so that by 2 to 3 months the majority of patients are seronegative (Vaughn 2000). In this case series the dengue infection could have occurred concurrently while the patients were also suffering from enteric fever, or even 2-3 months before they developed the disease. Result of the HI test in case number four supported the evidence of primary infection.

Symptoms and signs of dengue infection, especially during the acute phase of illness, are difficult to distinguish from other illnesses found in tropical areas. The differential diagnosis should include measles, rubella, influenza, typhoid, leptospirosis, malaria, other viral hemorrhagic fevers, and any other disease that may present in the acute phase, as a nonspecific viral syndrome (Gubler 1998, Isturiz 2000). There is no pathognomonic sign or symptom for DHF during the acute phase. Children frequently have concurrent infection with other viruses and bacteria causing upper respiratory symptoms (Gubler 1998).

None of the patients in this series experienced hemorrhagic manifestation. Unfortunately tourniquet test was not performed, which in case 4, with fever for only 4 days when admitted, this test should belong to the diagnostic steps which if positive, indicates increased capillary fragility. Haemoconcentration, with an increase of haematocrit of 20% was seen in case 4, although the child had anemia (hemoglobin 9.9 g/dl, haematocrit 30% at admission, and hemoglobin 8.8 g/dl, hematocrit 25% when repeated during convalescens). Liver enlargement was seen in all cases, which could have been related to either typhoid fever (Gomez 1998) or dengue infection (Mohan 2000). Moreover 3 of the patients were malnourished, which in turn might also have disturbance of the liver. Abnormal ALT and AST were seen in two cases (case 3 and 4).

Enteric fever usually is caused by *S. typhi* and, less often, other invasive *Salmonella*, including *S. paratyphi* and *S. choleraesuis*. The onset of symptoms is insidious. After an incubation of 10-14, which tends to be somewhat shorter in paratyphoid fever, fever, malaise, anorexia, and abdominal pain develop over a 2-to 3-day period. The fever rises in small increments, usually reaching 40<sup>0</sup> to 40.5<sup>0</sup> C by the end of the first week of illness. The temperature does not return to normal but rather rises to higher peaks each afternoon, with higher nadirs each subsequent morning during the first week. Eventually, the fever is unremitting; there are spikes in temperature without any return to normal (Gomez 1998). In contrast, dengue virus infection in humans causes a spectrum of illness ranging from inapparent or mild febrile illness to severe and fatal hemorrhagic disease. In a typical case of dengue fever, the patient experiences high fever, which in the first 2 days may be preceded by erythematous mottling and chills and may last for 5 to 7 days. Concomitantly, a severe frontal and retro orbital headache, myalgias, especially lower back, arm, and leg pains, arthralgias, especially in shoulders and knees, a prostrating weakness, and anorexia are clinical complaints (Hayes 1992). In typhoid fever, a dull, continuous frontal headache begins during the first 2 days of fever; Children commonly complain of

headache; they often are drowsy, irritable or delirious. Mild arthralgia involving multiple joints and vague, poorly localized back pain may occur (Gomez 1998). Constipation is more common than diarrhea; it occurs in about 50 per cent, while diarrhea occurs in about 30 per cent of typhoid patients (Gomez 1998). In dengue fever, constipation is occasionally reported; diarrhea and respiratory symptoms are frequently reported and may be due to concurrent infections (Gubler 1998). Prominent temperature and/or pulse dissociation is a well-known feature of typhoid but it is not unique (Richens 2000); it may also occur in dengue fever (Gubler 1998).

In this series prominent clinical features included anorexia, abdominal pain, nausea, vomiting, and liver enlargement (table 1). Diarrhea was seen in 2 patients, constipation in 2, and CNS disturbance in 2 patients, one with lethargy and delirium, the other with apathy. All these symptoms may be encountered in typhoid fever as well as dengue virus infection; however, since dengue infection may also be inapparent it would be very hard to determine when the dengue infection took place. Another possibility exists, namely that result of the Dengue Rapid Test in the three cases who showed evidence of IgM against dengue but were negative for the hemagglutination-inhibition assay, could have been false positive, since the rapid test showed low cross-reactivity at the IgM and not the IgG level in patients with malaria, leptospirosis, and typhoid (Lam 1998). A crosscheck using a more specific test would be the solution for this problem.

## SUMMARY

Four cases of bacteriological-proven typhoid fever have been reported. Because these cases served as controls in a study on Immunochromatographic Dengue Rapid Test, they were tested for the presence of IgM and IgG against dengue. The evidence of IgM encountered indicated recent dengue virus infection, within the last 2-3 months. Only one case was positive when the hemagglutination-inhibition assay was applied, while the other three were negative. One has to admit that the possibility of a false positive result of the Dengue Rapid Test remained to be taken into consideration, and a crosscheck using a more specific test would be advisable.

## REFERENCES

- Anonymous, 1997. Dengue Haemorrhagic Fever. Diagnosis, treatment, prevention and control. 2<sup>nd</sup> ed. WHO, Geneva, Switzerland
- Gomez HF, Cleary TG. *Salmonella*. In Feigin: Textbook of Pediatric Infectious Diseases 4<sup>th</sup> ed., Copyright © 1998 W.B. Saunders Company pp 1321-34. MD Consult-Book Text <http://home.mdconsult.com/das/book/body/87551933/987/174.html> 2/27/02
- Gubler DJ, 1998. Dengue and Dengue Hemorrhagic Fever. Clin Microb Rev; 11(3): 480-96
- Hayes EB, Gubler DJ, 1992. Dengue and Dengue Hemorrhagic Fever. Pediatr Infect Dis J; 11:311
- Isturiz RE, Gubler DJ, del Castillo JB, 2000. Dengue and Dengue Hemorrhagic Fever in Latin America and the Caribbean. Infect Dis Clin North Amer; 14(1): 121-40
- Lam SK, Devine PL, 1998. Evaluation of capture ELISA and rapid immunochromatographic test for the determination of IgM and IgG antibodies produced during dengue infection. Clin and Diagn Virol; 10(1):75-81
- Mohan B, Patwari AK, Anand VK, 2000. Hepatic Dysfunction in Childhood Dengue Infection. J Trop Pediatr; 46:40-3
- Olopoenia LA, 2000. Widal agglutination test – 100 years later; still plagued by controversies. Postgrad Med J; 76(892): 80-4. Abstract
- Richens J. Typhoid Fever. In: Armstrong: Infectious Diseases, First Edition, Copyright © 2000 Mosby, Inc. MD Consult-Book Text <http://home.mdconsult.com/das/book/body/87551933/1005/226.html> 2/27/02
- Stephens I, Levine MM, 2002. Concise reviews of Pediatric Infectious Diseases. Management of typhoid fever in children. Pediatr Infect Dis J; 21(2): 157-8
- Suh K, Kozarsky PE, Keystone JS, 2000. Evaluation of fever in the returned traveler. Medical Clin North Amer; 83(4): 997-1017
- Vaughn DW, Green S. Viral febrile illnesses. In: Strickland: Hunter's Tropical Medicine and Emerging Infectious Diseases, 8<sup>th</sup> ed., Copyright © 2000 W.B. Saunders Company pp 240-5. MD Consult-Book Text. <http://home.mdconsult.com/das/book/body/90506126/989/139.html> 3/12/02