

# Hanta Virus Infection During Dengue Virus Infection Outbreak in Indonesia

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## ABSTRACT

**Aim:** to investigate which recent infection could have caused the present dengue-like symptoms, in adult patients clinically fulfilling the WHO criteria for dengue, in which serologically were not confirmed for dengue virus infections.

**Methods:** prospective study. During an outbreak of dengue (between May 1995 and May 1996) 118 consecutive adults ( $\geq 13$  years) suspected by the WHO 1997 case definition of DF or DHF were investigated. Patients were examined for history of illness, physical and laboratory findings consisting of full blood counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), liver function (bilirubin, ASAT, ALAT), renal function (creatinine), and serological assays included dengue, hantavirus, chikungunya, *R. typhi*, *R. tsutsugamuchi*, rubella virus, influenza A virus, and leptospira.

**Results:** in 58 of the total 118 patients, recent dengue virus infection was serologically confirmed. In 20 of the remaining 60 patients, we found serological evidence of another recent infection: hantavirus (5), chikungunya virus (2), *R. typhi* (5), *R. tsutsugamuchi* (2), rubella virus (3), influenza A virus (1), and leptospira (2). No evidence for recent infection with any of the mentioned agents was detected in the remaining 40 specimens.

**Conclusion:** we conclude that based on clinical characteristics alone, it is not easy to diagnose dengue. Specific laboratory tests to differentiate dengue from other febrile illnesses are needed. Among these, in Indonesia hantavirus infection should be considered as well.

**Key words:** hantavirus, dengue virus infection, rickettsia, chikungunya.

## INTRODUCTION

Indonesia has a tropical climate and humidity which is conducive to perpetuation of *Aedes aegypti*, the main vector of dengue. Dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae* and may cause a wide spectrum of illness: asymptomatic infection, dengue fever (DF) and dengue hemorrhagic fever (DHF).<sup>1</sup> Clinical signs and symptoms of dengue fever are not specific and include sudden onset of fever, weakness, headache, joint pain, muscle pain, retro-orbital pain, nausea, vomiting, and rash. The less severe grades of DHF (grade I and II) manifest similar to DF with signs of spontaneous bleeding, and are difficult to distinguish from other viral illnesses found in tropical areas such as chikungunya virus infection (which is also transmitted by *Ae. Aegypti*), influenza, mild hantavirus infection and rubella, as well as bacterial infections such as mild leptospirosis and rickettsiosis.<sup>1-7</sup>

Epidemiological studies have demonstrated that during outbreaks of dengue 10.5% to 42.7% of cases can be detected by virus isolation,<sup>8,9</sup> 46.3% by IgM/IgG ELISA,<sup>9</sup> 41.8% by hemagglutination inhibition (HI) tests,<sup>10</sup> 41.4 to 66% by IgM ELISA and/or virus isolation,<sup>11,12</sup> and 73% by HI and/or virus isolation.<sup>13</sup> Thus, the rest of these patients may actually suffer from another febrile illnesses. Alternatively, the sensitivity of tests used may have been low, or a wrong sampling time-point for the test was used.

We studied a group of patients >13 years clinically suspected of recent dengue virus infection, of whom some were confirmed serologically but others not. We asked the question which other infectious agents could

be the cause of their present illness in the remaining patients. Since infections with chikungunya virus, hantavirus, *Rickettsia typhi*, *R. tsutsugamushi*, leptospira, rubella virus and influenza virus may present with the same clinical characteristics as dengue and may be encountered in Indonesia, the specimens were examined for serological evidence of these infections. We also investigated whether clinical symptoms and signs may help to differentiate between these infections.

## METHODS

### Patients and Data Collection

The study was performed in Dr. Kariadi Hospital, the university hospital of Diponegoro University, Semarang, Indonesia. Between May 1995 and May 1996, during an outbreak of dengue, 118 consecutive adults (>13 years), clinically suspected by the WHO 1997 case definition<sup>(1)</sup> of DF or DHF, were examined prospectively.

Of each patient, data were collected on a clinical record form, listing for each patient during hospital stay: name, age, sex, history of illness (date of onset of disease and date of admission), symptoms, physical findings and laboratory findings, including blood tests for cell counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), liver function (bilirubin, ASAT, ALAT), renal function (creatinine). Chest x-ray, ECG and ultrasonography were not done routinely.

For serological assays, 4 ml of blood was collected in vacutainer tubes (Becton Dickinson, Rutherford, NJ 07417) on the day of admission, on the day of discharge, and a week after discharge. The third specimen was omitted when the second specimen was two weeks or more after the first. Specimens were kept at minus 80°C until assayed.

### Serological Assays

All assays were performed at the virology laboratory of Erasmus University Hospital, Rotterdam, The Netherlands. Air transport of the samples from Semarang to The Netherlands was done on dry ice.

Samples were tested for the presence of specific antibodies against dengue virus by IgM capture/IgG enzyme linked immunosorbent assay (ELISA).<sup>14</sup> A recent dengue infection was diagnosed if IgM antibodies were demonstrated or if a fourfold rise of IgG antibodies between admission and at least two weeks later was demonstrated. All samples in which no recent dengue virus infection was found, were tested for antibodies against chikungunya virus, hantavirus, influenza A virus, leptospira, and *Richettsia typhi*. For the detection of antibodies against chikungunya virus

(IgG), Hantavirus (IgM and IgG) and influenza A (IgA), different ELISA-based systems were used, as described previously.<sup>3,15-17</sup> A greater than two times rise of IgG antibody titer against chikungunya virus between admission and at least two weeks later, was considered to represent a recent infection. If IgM antibodies against hantavirus were detected in ELISA, those were confirmed by immunofluorescence (IFA); the presence of IgM antibodies plus confirmed by IFA, was considered to represent a recent infection. A rising IgA titer against influenza A between admission and at least two weeks later was considered to represent a recent infection with influenza A virus. For the diagnosis of leptospirosis a haemagglutination inhibition (HI) test was done.<sup>(18)</sup> Only seroconversion between admission and a sample of at least two weeks later was considered to represent recent infection. IgM antibodies against *R. typhi* were measured by immunofluorescence (INDX, Baltimore, USA); an antibody titer  $\geq 1:32$  was considered to represent recent infection.

The sera in which no evidence for a recent infection with dengue virus, nor with any of the above mentioned other agents were demonstrated, were tested for the presence of IgM antibodies against rubella virus, using a IgM capture assay (Organon Technika, Boxtel, The Netherlands) and for the presence of IgM antibodies against *R. tsutsugamushi* by immunofluorescence (INDX, Baltimore, USA; positive titer  $\geq 1:32$ ).

### Statistical Analysis

Continuous data were described as median (range) and nominal data were described in number (%). All statistical analyses were performed with SPSS for Windows version 9.0.

## RESULTS

### Patients with Confirmed Recent Dengue Virus Infection (n=58)

In 58 patients, recent dengue virus infection was serologically confirmed. According to the 1997 WHO criteria, the classification of the 58 patients were: DF (42), DHF I (4), DHF II (7), DHF III (4), DHF IV (1). Their median age (range) in years was 19 (14-53) and sex ratio (M/F) 28/30.

### Patients without Serological Evidence of Recent Dengue Virus Infection (n=60)

On clinical grounds, the remaining 60 patients had been classified as follows: DF (49), DHF I (4), DHF II (6) and DHF III (1). In all but 4 patients, dengue specific IgG was found, but there was no rise for titer, indicating dengue virus infection in the past. In 20 of the

60 patients, we found serological evidence of another recent infection: hantavirus (5), chikungunya virus (2), *R. typhi* (5), *R. tsutsugamushi* (2), rubella virus (3), influenza A virus in (1), and leptospira (2). No evidence for recent infection with any of the mentioned agents was detected in the remaining 40 specimens. Evidence for infection with chikungunya virus in the past was found in 12 patients (IgG antibodies, but no rising titer). Three of these 12 patients had recent infections with dengue virus (1), hantavirus (1), and *R. typhi* (1). Also, evidence for hantavirus infection in the past was found in two patients.

### Clinical Characteristics

Table 1 shows the distribution of clinical variables of 58 patients with confirmed recent dengue and 20 with evidence of recent infection with chikungunya virus, hantavirus, *R. typhi*, *R. tsutsugamushi*, rubella virus, influenza A virus or leptospira. Headache, weakness, joint and/or muscle pain, epigastric pain, nausea, vomiting, were the most commonly presented symptoms/signs in all patients regardless of their final diagnosis. Bleeding manifestations were usually mild consisting of petechiae, gum bleeding and epistaxis. Hematemesis and/or melena were found in some patients with dengue and one with hantavirus infection classified on admission as DHF III. One patient with confirmed recent dengue virus infection (DHF IV) died, the remaining 117 patients recovered fully after a hospital stay of 2 to 18 days (median 6 days).

### Laboratory Results

As shown in table 2 the median levels of hemoglobin, haematocrites and leukocytes were normal in all cases. Marked thrombocytopenia was found in patients with dengue and in some patients with hantavirus and *R. tsutsugamushi* infection. A prolongation of coagulation parameters was seen in some patients with dengue (aPTT, PT), chikungunya (PT), hantavirus infection (aPTT) and *R. typhi* infection (PT). A mild to moderate elevation of ASAT and ALAT were found in dengue virus infection and in some patients with rubella virus, hantavirus, chikungunya virus and *R. typhi* infection. A moderate increase of creatinine (up to 4.3 mg/dl) was found in some patients with dengue virus infection. Three of five patients with hantavirus infection had proteinuria and microscopic hematuria, but in all of them serum creatinin was normal.

### DISCUSSION

In 114 of 118 (97%) adult patients clinically suspected of dengue virus infection by the 1997 WHO criteria, antibodies to dengue virus were found. This shows the high endemicity of dengue in the area of study. However, only in 58 patients, the clinical suspicion of dengue virus infections could be confirmed serologically. In 20 of the remaining 60 patients who presented dengue-like illness, a recent infection with hantavirus, chikungunya virus, *R. typhi*, *R. tsutsugamushi*, rubella

**Table 1. Clinical characteristics of 58 patients with confirmed dengue and 20 patients with serological evidence of recent hantavirus, chikungunya virus, *R. typhi*, *R. tsutsugamushi*, rubella virus, influenza A or leptospira infection**

Characteristics	Dengue (n=58)	Hanta (n=5)	Chikung. (n=2)	<i>R. typhi</i> *) (n=5)	<i>R. tsutsu</i> *) (n=2)	Rubella (n=3)	Influ. A (n=1)	Lepto. (n=2)
Median age (years)	19	15	26.5	16	27.5	19	46	19
Male/Female ratio	28/30	1/4	1/1	2/3	0/2	0/3	0/1	0/2
<i>Symptoms</i>								
Headache	57/58	5/5	0/2	5/5	2/2	2/3	1/1	2/2
Weakness	51/58	4/5	2/2	5/5	2/2	3/3	1/1	2/2
Joint/muscle pain	40/58	4/5	1/2	1/5	2/2	3/3	0/1	1/2
Nausea/vomiting	49/58	4/5	2/2	5/5	2/2	2/3	1/1	1/2
Epigastric pain	45/58	4/5	1/2	3/5	1/2	3/3	0/1	1/2
Retro-orbital pain	10/58	1/5	0/2	0/5	0/2	3/3	0/1	0/2
<i>Signs</i>								
Exanthema (rash)	13/58	2/5	0/2	0/5	0/2	2/3	0/1	0/2
Pharyngitis	7/58	0/5	1/2	0/5	0/2	1/3	0/1	0/2
Lymphadenopathy	7/58	1/5	0/2	0/5	0/2	2/3	0/1	0/2
Hepatomegaly	8/58	2/5	0/2	1/5	0/2	1/3	0/1	0/2
Petechiae	37/58	4/5	1/2	4/5	2/2	3/3	1/1	0/2
Epistaxis/gum bleeding	21/58	1/5	1/2	3/5	0/2	3/3	0/1	0/2
Hematemesis / melena	8/58	1/5	0/2	0/5	0/2	0/3	0/1	0/2

\*) None of these patients had an eschar.

**Table 2. Laboratory characteristics of 58 patients with confirmed dengue and 20 patients with serological evidence of recent hantavirus, chikungunya virus, *R. typhi*, *R. tsutsugamushi*, rubella virus, influenza A or leptospira infection**

	Dengue (n=58)	Hanta (n=5)	Chikung. (n=2)	R.typhi (n=5)	<i>R. tsutsu.</i> (n=2)	Rubella (n=3)	Influenza (n=1)	Leptospira (n=2)
Hb (g/dl)	13.6 (5.1-17.5)	12 (10.6-13.7)	13.2 (12.8-13.6)	12.4 (11.7-14.4)	11.6 (11.3-11.9)	12.8 (11.9-13.7)	12.6	12.2 (11.5-13.0)
Hct (%)	42.6 (15.8-54)	37.7 (34.0-41.7)	40.7 (40.7-40.8)	39.2 (34.8-44.7)	36.1 (33.9-38.4)	38.3 (36.6-43.0)	38.5	38.0 (35.8-40.3)
WBC (x10 <sup>9</sup> /L)	4.2 (1.4-18.7)	5.3 (3.6-6.3)	9.7 (2.9-16.6)	5.7 (5.6-8.6)	9.1 (5.8-12.4)	4.4 (3.3-6.4)	2.8	5.0 (4.3-5.7)
Platelets (x 10 <sup>9</sup> /L)	76 (17-255)	155 (24-267)	174.5 (131-218)	183 (52-204)	122.5 (35-210)	68 (60-161)	155	198 (189-208)
aPTT (sec)	39.4 (24.3-199.6)	41.6 (28-50.5)	32.5 (30.1-35.6)	33.7 (30.4-38.0)	38.4 (57.2-39.6)	30.7 (24.5-37.3)	30.2	31.4 (24.5-38.3)
PT (sec)	12.7 (10.5-28.4)	13.3 (12.1-14.4)	15.3 (14.6-16.0)	13.3 (12.3-16.4)	13.1 (12.3-13.9)	12.0 (11.9-14.2)	10.7	11.6 (11.5-11.7)
Bilirubin (mg/dl)	0.59 (0.13-1.9)	0.53 (0.46-1.32)	0.72 (0.35-1.1)	0.61 (0.42-0.67)	0.50 (0.36-0.64)	1.09 (0.53-1.63)	0.1	0.37 (0.36-0.39)
ASAT (u/l)	33.5 (7-225)	15.0 (3.0-56.0)	22 (17-27)	17.0 (8.0-76.0)	9.5 (8.0-11.0)	11 (10-214)	12.0	16 (11-21)
ALAT (u/l)	20.5 (4-107)	17.0 (6.0-27.0)	39 (13-65)	19.0 (6.0-59.0)	13.0 (7.0-19.0)	10 (9-11.0)	12.0	17.5 (12.0-23.0)
Creatinine (mg/dl)	0.9 (0.6-4.3)	0.8 (0.6-0.93)	1.05 (0.8-1.3)	0.9 (0.63-1.14)	0.83 (0.78-0.89)	0.92 (0.76-0.92)	0.8	0.84 (0.77-0.92)

Values are median (range); APTT control: 31.9 (30.1-38.6); PT control: 12.0 (11.1-13.7); Normal values: ASAT: 0-18 u/l; ALAT: 0-22 u/l; creatinine: <1.1 mg/dl

virus, influenza A virus, or leptospira was demonstrated. The clinical symptoms and signs of these 20 patients (table 1) were very similar to those of the 58 patients whose present illness was due to dengue. Most of these patients had mild dengue virus infection (DF or DHF I or II). Our findings in adult patients with suspected dengue contrasted with those in 50 children with dengue shock syndrome (DHF III or DHF IV), in whom the diagnosis dengue virus infection was confirmed in all cases.<sup>19</sup> The explanation probably is that the clinical picture of severe dengue virus infection (DSS) is more specific.

IgM antibodies against hantavirus were detected in 5 patients indicating recent infection, and in two patients with IgG with no rising titer indicating infection in the past. On admission, four of these five patients with recent hantavirus infection were clinically diagnosed as DF, whereas one patient had a more severe clinical presentation, and was originally diagnosed as DHF III. None of these patients had traveled outside Indonesia. These are the first reported hantavirus infections in humans from Indonesia. Hantavirus infection may manifest as mild or severe disease. The different hantavirus types are associated with different types of disease manifestations, both in terms of target organs

and disease severity.<sup>(20)</sup> Severe disease may manifest itself as Hantavirus Pulmonary Syndrome (HPS) or Hemorrhagic Fever with Renal Syndrome (HFRS). HPS may present as a non-specific illness with fever, myalgia, headache, and gastrointestinal symptoms, followed by a non-productive cough, culminating rapidly in respiratory insufficiency. Severe HFRS is characterized by extreme albuminuria and impaired renal function.<sup>21-24</sup> Three of five patients with hantavirus infection had proteinuria and microscopic hematuria for several days, but no impaired renal function.

We demonstrated antibodies against chikungunya in 14 patients but only in two patients the antibody profile indicated recent infection. On admission, these two patients were clinically diagnosed as DF and DHF I. Chikungunya is difficult to differentiate from DF or mild DHF due to the overlap in clinical symptoms and signs (table 2) as also was described previously.<sup>1,3,25</sup>

We detected IgM antibodies against *R. typhi* in 5 patients. This disease is known to occur in Indonesia.<sup>26-28</sup> Our five patients had mild rickettsiosis and had clinically been suspected of DF. Antibodies against *R. tsutsugamushi* were found in 2 patients. The clinical characteristics and laboratory finding of *R. tsutsugamushi* were similar to those of *R. typhi* infection.



We detected IgM antibodies against rubella virus in 3 patients. These patients were originally diagnosed as DF in one and DHF II in two patients. A similar finding has been reported previously.<sup>29</sup>

Antibodies against influenza A virus were found in one patient, clinically diagnosed as DF on admission. Also previous studies demonstrated that influenza can mimic mild dengue infection.<sup>4,30</sup>

We found antibodies against leptospira in two patients. Manifestations of leptospirosis may vary from a mild flu-like illness to an acute life-threatening condition with renal failure (Weil's disease). Our two patients had mild leptospirosis and were mistaken for DF on admission. Both dengue and leptospirosis are endemic in Indonesia. During a large outbreak of leptospirosis in Salvador, Brazil, 42 percent of cases were misdiagnosed as dengue fever in the outpatient clinic.<sup>6</sup> Also, substantial misdiagnosis of dengue and leptospirosis occurred in Barbados. During 1995, 48 of 108 sera and during 1996, 21 of 64 sera from leptospirosis-negative patients were found to have IgM antibodies to dengue virus.<sup>5</sup> On the other hand, after hurricane-generated floods in Puerto Rico, leptospirosis was diagnosed in patients suspected clinically of dengue, but testing dengue-seronegative.<sup>31</sup>

In the remaining 40 patients, we failed to demonstrate the presence of another recent infection. This may be due to the presence of yet another disease, not tested for. For instance, in patients clinically suspected of dengue, typhoid fever with a positive culture for *Salmonella typhi* (Hadinegoro SR, unpublished), and measles<sup>32</sup> have been diagnosed.

We did not test for Japanese encephalitis, also caused by a flavivirus, but none of the patients had any manifestations of this disease, which in most cases runs a severe course and is often fatal. The other flavivirus causing Yellow Fever does not occur in Indonesia.

## CONCLUSION

It is difficult to clinically distinguish dengue from other febrile illnesses. This applies particularly to dengue fever and the milder grades of dengue hemorrhagic fever (DHF I and II) in adults. Which specific laboratory tests are to be used depends on the geographical distribution of diseases. Differentiating other infectious agents not only is of epidemiological but also of clinical interest, because adequate antibiotic treatment can be instituted in some of these infections, reducing morbidity and mortality. Hantavirus infection should be added to the differential diagnosis of dengue virus infection in Indonesia.

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