Vertical Transmission of Dengue

Joon K. Chye, Chin T. Lim, Kwee B. Ng, Jason M. H. Lim, Rebecca George, and Sai K. Lam

Dengue, an important mosquito-borne flavivirus infection, is endemic in Southeast Asia. We describe two mothers who had acute dengue 4 and 8 days before the births of their infants. One mother had worsening of her proteinuric pregnancy-induced hypertension, liver dysfunction, and coagulopathy and required multiple transfusions of whole blood, platelets, and fresh frozen plasma. Her male infant was ill at birth, developed respiratory distress and a large uncontrollable left intracerebral hemorrhage, and died of multiorgan failure on day 6 of life. Dengue virus type 2 was isolated from the infant’s blood, and IgM antibody specific to dengue virus was detected in the mother’s blood. The second mother had a milder clinical course; she gave birth to a female infant who was thrombocytopenic at birth and had an uneventful hospitalization. Dengue virus type 2 was recovered from the mother’s blood, and IgM antibody specific to dengue virus was detected in the infant’s blood. This report highlights not only the apparently rare occurrence of vertical transmission of dengue virus in humans but also the potential risk of death for infected neonates.

Case Reports

Case 1

A 25-year-old pregnant Malay woman (gravida 2, para 0) who had no history of major medical illness was admitted to the hospital at 36 weeks’ gestation in June 1996 for stabilization of proteinuric pregnancy-induced hypertension (blood pressure, 160/100 mm Hg). Two days after her admission, she developed an acute fever (temperature, 39.4°C) with no obvious clinical focus. The fever gradually abated over the next 72 hours with paracetamol treatment. She had generalized edema and an enlarged liver (2 cm) but no petechiae. Transient mild bleeding of the gums and easy bruising at venipuncture sites were noted on day 5 of illness.

Received 26 March 1997; revised 11 July 1997.
Reprints or correspondence: Dr. Joon Kin Chye, Department of Pediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
Clinical Infectious Diseases 1997;25:1374–7
© 1997 by The University of Chicago. All rights reserved.
1058–4838/97/2506–0014$03.00
isolated from the first sample when mosquito larva inoculation [7] and AP-61 mosquito cell cultures were performed [8]. Viral nucleic acid was not detected in the serum by reverse transcription (RT) PCR analysis with dengue virus–specific primers [9]. Hemagglutination inhibition (HI) tests [10] performed on paired serum samples showed only a twofold rise in titers from 1:80 to 1:160 (table 1).

The Apgar scores for the infant were 6/10 and 7/10 at 1 and 5 minutes, respectively. No resuscitation was required. However, he appeared pale and was grunting soon after birth; he was promptly admitted to the special care nursery after a routine intramuscular dose of vitamin K was administered. At 12 hours of life, he was intubated and received ventilatory support because of increasing oxygen requirement and respiratory distress. The ventilatory support needed was minimal, and he was extubated 24 hours later and received oxygen in a head box. Mild, nonspecific, generalized streaky changes were noted on his chest radiograph. His initial CBC count showed a hemoglobin level of 189 g/L, a hematocrit of 58%, and a WBC count of 10.8 x 10⁹/L. Coagulation previously. Her temperature had peaked at 39.4°C, irritability, and opisthotonus. A lumbar puncture was performed, and a traumatic tap revealed heavily blood-stained fluid, for which a traumatic tap was considered the most likely cause. A WBC count in the CSF was normal. At this stage, intravenous penicillin and gentamicin therapy was started.

A transient generalized blanchable red rash was noted at the end of the first day. At 36 hours of life, he started to have episodes of low grade fever (temperature, <38°C), irritability, and opisthotonus. A lumbar puncture was performed, and a second blood specimen for culture was obtained. CSF analysis revealed heavily blood-stained fluid, for which a traumatic tap was considered the most likely cause. A WBC count in the CSF could not be determined, but the sugar and protein levels in the CSF were normal. At this stage, intravenous penicillin and gentamicin therapy was changed to intravenous cloxacillin and amikacin therapy. Another CBC count revealed a hemoglobin level of 116 g/L, a hematocrit of 34%, a WBC count of 7.3 x 10⁹/L, and a platelet count of 165 x 10⁹/L. Since sepsis was suspected, a blood specimen for culture was obtained, and intravenous penicillin and gentamicin therapy was started.

Findings on a cranial ultrasonographic scan obtained at 50 hours of life were unremarkable. At 60 hours of life, the infant developed more respiratory difficulties, and ventilatory support was started again because of frequent desaturations. Another chest radiograph showed bilateral, generalized, patchy perihilar opacities. Intravenous cloxacillin therapy was stopped, and intravenous imipenem and cefotaxime were added to the therapeutic regimen because the possibility of meningitis was entertained. A posttransfusion CBC disclosed a hemoglobin level of 127 g/L, a hematocrit of 37%, a WBC count of 7.7 x 10⁹/L, and a platelet count of 12 x 10⁹/L; these findings necessitated a further platelet transfusion. Another lumbar puncture again yielded heavily blood-stained CSF. A second cranial ultrasonographic scan obtained at 90 hours of life demonstrated a massive left intracerebral hemorrhage with a midline shift that was causing obliteration of the left lateral ventricle and dilatation of the right lateral ventricle.

Over the next 2 days, the infant developed severe acute renal failure, hypotension, seizures, hypoglycemia, abnormal liver function, and coagulopathy. Despite the maximal intensive supportive care, the infant’s condition continued to deteriorate rapidly, and he finally died on day 6 of life. A postmortem examination was declined by the family. Both sets of blood cultures and the CSF cultures were negative for bacterial growth. Dengue virus type 2 was isolated from a blood specimen obtained on day 2 of life; this isolation was confirmed by RT PCR analysis. However, IgM antibody specific to dengue virus was not detected in blood specimens obtained on days 2 and 6 of life. Similarly, the HI tests did not show any change in the low titers of antibody to dengue virus.

Case 2

A 31-year-old pregnant Malay woman (gravida 5, para 4) was admitted to the hospital at 38 weeks’ gestation in August 1996 because of fever and mild dysuria. Her husband had been admitted to another hospital because of dengue fever 2 months previously. Her temperature had peaked at 39.4°C on the day of admission, and the fever gradually subsided over the subsequent 48 hours. A urine culture was negative for bacterial growth. Treatment with intravenous ampicillin and oral nitrofurantoin was stopped after 10 days. The initial CBC showed a hemoglobin level of 123 g/L, a WBC count of 10.8 x 10⁹/L, and a platelet count of 125 x 10⁹/L, respectively. No resuscitation was required.

Table 1. Summary of data from two cases of vertical transmission of dengue.

<table>
<thead>
<tr>
<th>Case, patient</th>
<th>HI titer (days of paired serum sampling)</th>
<th>IgM antibody</th>
<th>Virus isolated</th>
<th>RT PCR analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>1:80 to 1:160 (4 and 10)*</td>
<td>Positive</td>
<td>None</td>
<td>Negative</td>
</tr>
<tr>
<td>Infant</td>
<td>1:10 to 1:10 (2 and 6)*</td>
<td>Negative</td>
<td>Dengue virus type 2</td>
<td>Positive</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>1:10 to 1:2,560 (2 and 6)*</td>
<td>Positive</td>
<td>Dengue virus type 2</td>
<td>Positive</td>
</tr>
<tr>
<td>Infant</td>
<td>1:160 to 1:320 (1 and 11)*</td>
<td>Positive</td>
<td>None</td>
<td>Negative</td>
</tr>
</tbody>
</table>

NOTE. HI = hemagglutination inhibition test; RT = reverse transcription.
* Days of illness.
† Days of life.
and a platelet count of $187 \times 10^9$/L. The platelet count had dropped to $81 \times 10^9$/L on day 3 of her illness. On day 8, platelets were transfused because she developed generalized petechiae with severe thrombocytopenia (platelet count, $11 \times 10^9$/L).

Although the platelet count increased the next day to $42 \times 10^9$/L, she had epistaxis, which was controlled with further platelet transfusions. She also went into spontaneous labor; a live female infant weighing 3.0 kg was delivered vaginally on day 9 without any complications. The postpartum period was uneventful. Results of liver function tests and coagulation analysis were normal. She was discharged after 13 days of hospitalization.

Dengue virus type 2 was detected in the blood sample obtained on day 2 of her illness; this isolation was confirmed by RT PCR analysis. Only the second blood sample, obtained on day 6, was positive for IgM antibody specific to dengue virus. The HI tests on paired serum samples showed a large rise in titers from 1:10 to 1:2,560.

Given the confirmed diagnosis of maternal dengue fever and the death of the infant in the previous case, the infant was admitted to the special care nursery immediately after birth for close observation, even though her condition at birth was good (Apgar scores were 9/10 and 10/10 at 1 and 5 minutes, respectively). She had a palpable 1-cm liver edge at the time of admission, flushed skin at 24 hours of age, and slightly diminished peripheral perfusion on day 3. A low-grade fever (maximum temperature, 38.4°C), which lasted for 24 hours, was noted on day 4. Intravenous penicillin and gentamicin therapy for presumed sepsis was started, but this therapy was stopped when the blood cultures yielded no organisms. The infant remained clinically well.

The CBC on day 1 showed a hemoglobin level of 229 g/L, a WBC count of $30 \times 10^9$/L, and a platelet count of $50 \times 10^9$/L. Coagulation analysis was unremarkable: PT ratio, 1.0; APTT, 49.5 seconds. Transfusions with platelets and fresh frozen plasma were given. The platelet count rose transiently to $109 \times 10^9$/L the next day and then stayed at 60–63 $\times 10^9$/L for 2 days before gradually rising to $148 \times 10^9$/L on day 8. Liver function tests revealed the following: AST level, 108 U/L; ALT level, 32 U/L; alkaline phosphatase level, 183 U/L; and albumin level, 26 g/L. Serial cranial ultrasonographic scans obtained on days 1, 7, and 11, subsequent liver function tests, and a coagulation profile were unremarkable. The infant was discharged to home on day 11 of life.

IgM antibody specific to dengue virus was detected in blood samples obtained on days 6 and 11 of life but not in the two samples of blood (cord and peripheral venous blood) obtained on the day of birth. The HI tests showed a low rise in titers from 1:160 to 1:320. No virus was isolated from the acute-phase serum sample, and RT PCR analysis was negative.

**Discussion**

Perinatal transmission of dengue is evidently rare. Worldwide, only six newborn infants with infections due to dengue virus types 1 and 2 have been described in Tahiti and Thailand [4, 5]. All these infants had common clinical features of thrombocytopenia, fever, hepatomegaly, and varying degrees of circulatory insufficiency, which were also found in our two cases. However, case 1 deviates from the benign course reported for these six infants and our second case.

In retrospect, our first infant, who had signs of cerebral irritation on day 2 of life, may have had meningoencephalitis. There are increasing reports implicating the direct involvement of this virus in patients with neurological manifestations [11]. Unfortunately, the lack of a postmortem examination and the blood-contaminated CSF precluded the confirmation of this postulation. Alternatively, the marked irritability of the infant could have resulted from subarachnoid hemorrhages, as evidenced by blood in the CSF (the amount of which was not sufficiently large to be detected by the first cranial ultrasonographic scan). Subarachnoid hemorrhages, uncommon compared with hemorrhages in the gastrointestinal tract and skin, have been reported at autopsy for infants and children with acute dengue [12]. The severe intracerebral hemorrhage, which led to the later multiorgan dysfunction, was unexpected. The mildly prolonged coagulopathy (within the normal range for neonates), severe thrombocytopenia, and the underlying vasculopathy of this disease [13] may have initiated and caused the progression of the hemorrhage in this infant.

It is uncertain whether the early administration of platelets and fresh frozen plasma had any true protective value for our second infant because all six other reported cases had favorable outcomes without any intervention [4, 5]. The severity of the maternal dengue virus infection, a probable primary dengue virus infection in the mother, a delay in the laboratory confirmation of dengue in both the mother and the infant, and the poor condition of the infant at birth (case 1) were the main distinguishing features between our two cases; these factors may have been important contributors to the death of the first infant because the strain of the viruses in both cases was the same (type 2).

The serological features of these two cases are also interesting (table 1). In the first case, when the possibility of maternal dengue virus infection was raised on day 4 of illness, the mother had become afebrile. The failure to detect virus in her serum was thus a reflection of the short period of viremia that had passed, and seroconversion with IgM antibody to dengue virus had happened. The poor results of HI tests suggest that this infection was most likely primary dengue. In comparison, the dengue virus was recovered from her infant on day 2 of life and 6 days after the onset of the maternal fever (i.e., when the platelet count dropped and he became symptomatic). His lack of an IgM antibody response as well as the negative HI tests, probably reflects the short duration of his illness before his death.

In contrast, dengue virus infection was suspected early in the second mother; the blood tests were performed early in the mother’s febrile illness, thus accounting for the initial detection
of virus and the later appearance of IgM antibodies on day 6. The dramatic and rapid rise in the titers of IgM antibody to dengue virus that were measured by the HI tests indicates that this infection was most probably secondary dengue. Her infant, who was born 8 days after the start of the maternal fever, was thrombocytopenic at birth. Since both the virus and IgM antibody were not detected at birth, we postulate that the brief period of viremia had occurred while in utero and that the “window” period for seroconversion had included the day of birth. IgM antibody became detectable 6 days later. The mildly elevated titer of antibody to dengue virus that was detected at birth was probably due to maternal IgG antibody acquired transplacentally.

Except for the lack of rise in the hematocrit (≥20%) and the absence of pleural effusions (as demonstrated on a chest radiograph), the first mother had all the other features that fulfill the criteria of the World Health Organization [14] for classic adult dengue hemorrhagic fever. She had acute dengue virus hepatitis, bleeding tendencies, and clinical evidence of increased vascular permeability, as manifested by generalized edema, hypoalbuminemia (albumin level, 21 g/L), and ascites. The large volume of blood products and intravenous fluids that she received during the acute phase of her illness would have prevented the development of any hemoconcentration and possible circulatory shock. A chest radiograph was not obtained because of the absence of clinical indications, but normal respiratory status does not exclude asymptomatic pleural effusions (which are highly likely in the context of her clinical illness). It is unclear whether the existing criteria of the World Health Organization for dengue hemorrhagic fever is applicable to “nonclassic” cases, such as infected neonates, pregnant women (with or without complications of pregnancy), and individuals being monitored and treated early in the course of their illnesses.

Even though dengue virus infection is common in Malaysia, to date, there have not been any reported cases of vertical transmission of dengue to neonates in this country. It is anticipated that such cases would be underappreciated and underdiagnosed. Obstetric conditions, such as HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet counts), may confuse or mask the clinical manifestations of dengue virus infection—namely, deranged liver functions and thrombocytopenia. In neonates, other infections (bacterial, viral, or fungal) can cause clinical features and hematologic changes similar to those of dengue virus infection. The typical rash of dengue fever may be absent, and the occurrence of subclinical infections lends further confusion to the problem. A high index of suspicion is therefore required for the diagnosis, especially in areas of endemicity and during epidemic outbreaks. Thus, a proper epidemiological study is necessary to help understand and to delineate the extent of this potentially fatal disease.

In conclusion, vertical transmission of dengue virus may lead to a full-blown illness in the neonate similar to that seen in children and adult patients. An awareness, and hence early diagnosis and management, of this potentially lethal condition is necessary to reduce perinatal morbidity and mortality, especially in communities where dengue is endemic.

References