

CASE REPORT

VERTICAL TRANSMISSION OF DENGUE INFECTION: THE FIRST PUTATIVE CASE REPORTED IN CHINA

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SUMMARY

Dengue is a systemic viral infection that is commonly transmitted between humans via mosquitoes. Other modes of transmission such as the vertical one are rare and have been infrequently reported in the literature. This report investigates one case of vertical transmission of dengue in Guangzhou, China. A G1P1 lady at 39 weeks of gestation was referred to the Huzhong Hospital presenting a fever for two days. She subsequently developed a skin rash on the back and lower limb and at that time she had already experienced five days of fever. She subsequently went into labor and delivered a female neonate weighting 3,500 g at birth. The neonate developed fever on the third day of life which was associated with a systemic erythematous skin rash. There was no report or evidence of mosquito bites after birth. A complete blood count showed leucopenia, thrombocytopenia and anemia and the liver function test showed elevated AST, GGT and bilirubin. Dengue was diagnosed in the mother and the neonate by the ELISA dengue virus NS1 antigen test (Wantai, Beijing, China) and dengue virus fluorogenic quantitative PCR test (Liferiver, Shanghai, China). The case report illustrates the possibility of the vertical transmission of dengue. Clinicians should be alert to this possibility and institute early treatment. Further direct evidence and research are required.

KEYWORDS: Dengue; Vertical transmission.

INTRODUCTION

Dengue is a self-limiting systemic viral infection transmitted between humans via mosquitoes. Previously, dengue was stratified by disease severity into dengue fever, dengue hemorrhagic fever and dengue shock syndrome. However, recently, the classification has been revised and simplified, resulting in the terms dengue or severe dengue¹. Dengue is defined by the World Health Organization (WHO) as an acute febrile illness associated with two or more of the following signs or symptoms: intense headache, retro-orbital pain, myalgia, arthralgia, skin rash, leucopenia and hemorrhagic manifestations². In recent years, dengue has proven to be an increasingly serious global health challenge as the incidence of dengue has been rising with concomitant expansion of the endemic regions. The WHO estimates that about 2.5 billion people worldwide are at risk of dengue infection, with 50 to 100 million new cases annually, of which 500 thousand severe patients are treated as outpatients and about 25 thousand patients die³.

In China, dengue cases are mainly centered in the Guangdong province, which has ever since developed local public health efforts

to control dengue. In past years, there have been major outbreaks of dengue in Guangdong in 1995, 2002, 2006 and 2013, accounting for a major outbreak every 4-7 years. The latest outbreak has taken place in 2014, and at that time a total of 45,189 dengue cases were reported, with six deaths. In terms of epidemiology, although the four serotypes of dengue virus have already been reported in China, dengue virus type 1 is responsible for the majority of cases⁴.

Dengue during pregnancy may be associated with various maternal and neonatal complications. Regarding the maternal complications, the most severe form of dengue during pregnancy can lead to death. Other complications include perinatal death, miscarriage, low birth weight, preterm delivery and subsequent admission to the neonatal intensive care unit⁵⁻¹². Until now, all the reported cases of congenital dengue virus infection have occurred in neonates whose mothers were infected very late in pregnancy. Several studies indicate that intrauterine infection caused by dengue viruses can be proved by the virus isolation from fetal or cord blood samples¹³. Due to the fact that cases of vertical transmission of dengue have been infrequently reported globally¹⁴⁻²⁰, very little is known about this mode of transmission.

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CASE REPORT

A 25 year-old Chinese pregnant woman at 39 weeks of gestation was admitted to a general hospital complaining of fever (initial T_{\max} 37.8 °C) that rose to 39.2 °C and was associated with a mild erythematous skin rash. After admission, the patient progressed with arthralgia, myalgia, frontal headache, but without nausea or vomiting. A complete blood count revealed a white blood cell count of 5,560/mm³ (83.8% of neutrophils), C - reactive protein of 9.3 mg/L, procalcitonin of 0.14 ng/mL. On the second day of hospitalization, rupture of membranes was noticed and she underwent a cesarean delivery. Postoperatively, the fever persisted and was not relieved by the use of ibuprofen. She subsequently developed a skin rash on her back and lower limbs on the third day after the cesarean delivery, and this was not relieved by the use of a calcium gluconate injection as an anti-anaphylactic treatment. The patient was thereafter transferred to the Zhujiang Hospital, a reference center, in the 5th of October 2014. On admission she was afebrile with a heart rate of 84 bpm, a blood pressure of 88/66 mmHg and the respiratory rate was 18 with clear lungs on auscultation. The abdomen was soft, with mild epigastric tenderness. Neurological examination including the eye fundus was normal. There was no evidence of bleeding on the clinical evaluation. The complete blood count revealed a white blood cell count of 3,230/mm³ (neutrophils 58.9%), while the platelet count, hemoglobin, IL-6 and procalcitonin were 88,000/mm³, 11.8 g/dL, 11.8 ng/L and 0.1 ng/mL, respectively. The erythrocyte sedimentation rate, prothrombin time, urine analysis, serum creatinine, hepatic transaminases were all within normal limits and remained normal during the entire hospital stay. No focal lesions were observed on the chest X-ray. A clinical diagnosis of a viral fever or dengue was made based on the history and the physical examination. On the day of admission corresponding to the eighth day of fever, dengue virus infection was confirmed by the finding of a positive dengue virus NS1 antigen by ELISA and a seroconversion demonstrated by the presence of IgM and IgG anti-dengue virus. The dengue virus was serotype 1. All the blood samples were processed and tested in the Zhujiang Hospital Central Laboratory. The patient was treated according to the current national dengue management guidelines that preconizes fluid balance as well as the monitoring of blood pressure, blood parameters and bleeding. The white cell and platelet counts were checked every day. The fever disappeared after admission, the white cell has rapidly increased from 3,230/mm³ on day 1 to 10,7000/mm³ on day 2. The platelet count has also returned to normal. On day 3 she was discharged from hospital afebrile and clinically well, presenting normal white cell and platelet counts.

The neonate was female, weighting 3,500 g at birth, with an Apgar score of 9 at the 5th minute of life, and she appeared well at birth. The neonate has never left the maternity ward since birth, and had no history of mosquito bites after birth. She developed fever on day 3 after birth (T_{\max} 38.5 °C), a systemic erythematous skin rash on day 1 of fever, and the complete blood count revealed a white blood cell count of 8,420/mm³ with 60.9% of neutrophils. She was admitted to the neonatal intensive care unit of the Zhujiang Hospital on day 2 of fever. The complete blood count was checked every two days. Her hemoglobin decreased notably reaching the lowest value of 13.4 g/L, platelet count of 29,000/mm³ and white blood cell count of 1,308/mm³ (37.0% of neutrophils). The complete blood count variation is shown in Figure 1. Her liver function tests showed mildly elevated AST, a four-fold elevated γ GT and an eight-fold elevated bilirubin, meanwhile her ALT was normal. Two days

later, new liver function tests showed normal ALT, two-fold elevated AST, four-fold elevated γ GT and six-fold elevated bilirubin. The chest X-ray showed increased bronchovascular markings. The prothrombin time, urinalysis and serum creatinine were all within normal limits and remained normal during the entire hospital stay. On the third day of life, one blood sample of the neonate was collected and then dengue was confirmed through a positive dengue virus NS1 antigen test (ELISA). A seroconversion has not been confirmed due to absence of anti-IgM and IgG to dengue virus. On the fifth day of fever (8th day of life) another blood sample was collected and a positive dengue virus fluorogenic quantitative PCR result was reported. Serotype of Dengue virus serotype 1 was found. All of the samples were processed and tested in the Zhujiang Hospital Central Laboratory. During the hospital stay, the neonate had no clinical manifestations of intracranial hemorrhage and her blood pressure was normal. The neonate was finally diagnosed with dengue, neonatal jaundice, neonatal pneumonia and an atrial septal defect. It is not clear whether neonatal jaundice and neonatal pneumonia are related to dengue. It is unlikely that the atrial septal defect is related to the dengue infection. She was treated according to the current national dengue management guidelines and was afebrile by day 3 of fever when her skin rash began to disappear. Her treatment involved gamma globulin transfusion, plasma transfusion, anti-inflammatory and antipyretic drugs. When she was discharged from hospital, the neonate's clinical condition was fine but her body weight had fallen to 3,350 g. The neonate was followed up and her basic developmental milestones (weight, height, fine motor and language) were normal at the age of one. However, cranial ultrasounds to evaluate the occurrence of intracranial hemorrhages were not performed.

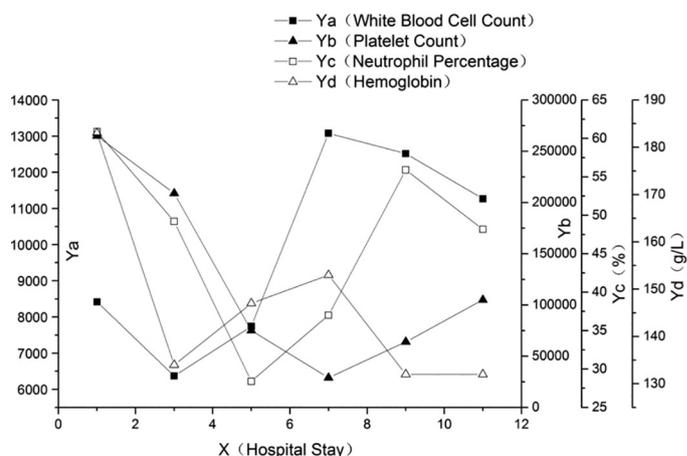


Fig. 1 - Hemogram was checked for the neonate after admission to Zhujiang Hospital. (a) White blood cell count trends; (b) Platelet count trends; (c) Neutrophil percentage trends; (d) Hemoglobin trends; X-axis represents the hospital stay in Zhujiang Hospital.

DISCUSSION

Several cases of vertical transmission of dengue showing the presence of dengue virus in fetal and cord blood samples have been reported worldwide, demonstrating the intrauterine acquisition of dengue infection^{13,21}. However, vertical transmission is not considered a common mode of transmission of dengue infection¹. Furthermore, the likelihood of vertical transmission when the mother is infected is low. To date, there have been no reports of congenital dengue infection in neonates born

to mothers infected early in pregnancy. A possible explanation is that maternal infections acquired near the time of delivery would not have had enough time for protective antibodies to be produced and transferred to the neonate, therefore conferring a passive immunity. The maternal viremia would therefore be transferred to the unprotected fetus²¹. Some reports have described variable neonatal outcomes, from asymptomatic infections to death.

Laboratory diagnosis is vital for dengue infections confirmation. Laboratory diagnosis can be performed through dengue virus isolation, dengue virus nucleic acid detection, NS1 antigen detection and the use of other serological methods. Samples for dengue virus detection must be taken within the first four to five days of infection, during the febrile phase. The NS1 antigen detection appears to peak about seven days after the onset of symptoms. IgM levels rise quickly and appear to be detectable from 3-5 days and then peak about two weeks after the onset of symptoms, then declining to undetectable levels over 2-3 months. IgG appears shortly after IgM though with very low levels at the beginning. Primary dengue infections are characterized by high levels of anti-dengue IgM and low levels of IgG²². In this case, the diagnosis of dengue in the mother was confirmed by the dengue virus NS1 antigen test (ELISA) and the diagnosis in the neonate was confirmed by both, the dengue virus NS1 antigen (ELISA) and the dengue virus fluorogenic quantitative PCR. Although we did not collect the neonate's cord blood samples which could act as a direct evidence of vertical transmission, the clinical manifestation and laboratory test results combined with the lack of antecedents of mosquito bites after birth gave us sufficient ground to formulate the suspicion of congenital, vertically transmitted dengue infection which has manifested in the neonatal period.

The case correlates well with other reported cases in the literature. Firstly, all reported cases of congenital dengue infections have occurred in neonates born to mothers infected very late in pregnancy. In this case, the mother developed fever at 39 weeks of gestation, and subsequently underwent a cesarean delivery. Furthermore, the latent period of dengue is between 3-15 days, more commonly between 5-8 days. In this sense, the earliest possible presentation of a primarily acquired neonatal dengue infection would have been on day four of the infants' life. In the review by Sirinavin (2004), the onset of fever in cases of vertically transmitted dengue virus infections varied from one to 11 days after birth, with an average of four days and the signs and symptoms lasted 1-5 days²³. In the present case report the neonate developed fever on day three of life, accompanied by a systemic erythematous skin rash that lasted for three days. Thus, it is highly unlikely that the neonate has acquired the infection via vectors and a vertical transmission is much more likely. Furthermore, almost all of the confirmed cases were reported during outbreaks in highly endemic areas such as Cuba, Brazil, Malaysia, and Thailand¹⁷⁻²⁰. The reason for this behavior is not clear, but maybe the outbreaks increase the likelihood of pregnant women to be infected. According to data released by the Guangdong Provincial Centre for Disease Control and Prevention, in 2014, the Guangdong province experienced a major outbreak of dengue with a total of 45,189 cases. Taking this information into account, the epidemiology of the present case is consistent with past results.

In conclusion, vertical transmission may be a probable mode of dengue infection. If a woman acquires dengue during pregnancy, clinicians should consider the possibility of vertical transmission, treat the mother and monitor the possible vertical transmission. During late

pregnancy, women can also consider the use of preventing measures such as more vigilance to avoid mosquito bites when they live in endemic areas so as to lower the risk of infection. Further direct evidence and research is required.

CONSENT

Written informed consent was obtained from the patient and the patient's legal guardian(s) for publication of this case report and the corresponding images.

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