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Congenital Dengue Infection: Are we missing the Diagnosis? Case report with review of literature

Congenital dengue infection: Are we missing the diagnosis?

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ABSTRACT

Neonatal dengue is now being increasingly reported for changing epidemiology and improved rapid detection methods. Vertical transmission with dengue virus is concordant with rules of nanomedicine and may present differently in newborns from what we normally see in older children. It may have prolonged symptomatology and protracted thrombocytopenia. There are no specific guidelines for neonatal dengue management. There is dearth of standard literature about neonatal dengue per se and most recommendations are based on experiences with older children and adults. The unique pathogen–host interaction complicates dengue vaccine development and creates provocative questions in vaccine development. We present a case report of neonatal dengue with review of literature. A day 8 old newborn with maternally acquired dengue was admitted in our NICU and had an eventful course. This congenital dengue infection case gives us good learning experiences in a not so well understood entity.

1. Introduction

Dengue is the most important tropical mosquito-borne infectious disease caused by an arbovirus, the dengue virus. After being bitten by a vector mosquito, human beings will obtain the dengue virus, which can result in infection. The dengue virus is a single-stranded RNA virus in the genus *Flavivirus* and family Flaviviridae. This virus is approximately 40–60 nm. There are four distinct serotypes of dengue virus that can cause disease. A high fever, accompanied by hemo-concentration and thrombocytopenia, is the hallmark of severe dengue disease.[1,2]

Concern regarding women who are pregnant becoming infected with dengue has been heightened in recent years due to an increase in adolescent and adult infections[3] Women of child-bearing age are now increasingly at risk of acquiring dengue infection while pregnant and may be more likely to develop severe disease as second infections occur later in life. DHF during pregnancy has not been shown to cause any congenital abnormalities however transmission from mother to fetus can cause perinatal mortality and morbidity.[4] In one study recent dengue infection was demonstrated in 2.5% of parturients, with a vertical transmission rate of 1.6%.[5]

DHF in the newborn may begin as a severe, non-specific illness and symptoms may not be present immediately after birth. Because symptoms in the newborn may be non-specific, a high degree of suspicion is needed.[6] We present a case report of newborn with congenital dengue which presented to us on day 8 of life with maternal positive dengue report.

2. Case report

A term male baby born to 29 year old Primi mother (out born) by normal vaginal delivery with birth weight 3.05 kg was admitted in our NICU on day 8 of life with history of fever for 1 day after being referred by a local pediatrician. Antenatal history was unremarkable. Apgars were normal at birth but baby developed tachypnea at 2 hour of birth and was treated at transient tachypnea of newborn. Baby was discharged to home on 3rd post-natal day with mother. Mother was readmitted in same hospital on 4th post-natal day with high grade fever and was diagnosed to have dengue fever by positive IgM Elisa test. She had severe thrombocytopenia (lowest platelet being 16,000/cmm) and recovered without any hemorrhagic manifestations.

Abbreviations: CRP, C reactive protein; CPAP, continuous positive airway pressure; I.V., intravenous; LFT, liver function test; RFT, renal function test; DSS, dengue shock syndrome; DHF, dengue hemorrhagic fever; ADE, antibody dependant enhancement; NS1, non-structural antigen 1; RT-PCR, reverse transcriptase polymerase chain reaction.

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The baby on admission to NICU had moderate fever (100.2 °F) and other normal vitals. Liver was 2.5 cm palpable under RCM and spleen tip just palpable. Lab tests revealed NS1 antigen positive and negative IgM/IgG Elisa. Platelet count was 1.1 lacs/cmm and CRP mildly positive (CRP-7 mg/L; normal range 0–6 mg/L) on admission. Baby was started on first line I.V antibiotics after drawing blood C/S and put full feeds with plan to repeat PCV and Platelet next day. Baby became afebrile next day and clinical examination was other unremarkable except for hepatosplenomegaly. Over next few days platelet count fell (minimum being 10,000/cmm on 11th day of life) and multiple platelet transfusions were given during this period (total 9 transfusion during hospital stay). In view of baby not completing feeds completely I.V. fluid was started on D3 of admission and platelets/PCV checked at regular intervals. On D4 of admission (11th post-natal day) baby developed respiratory distress and was started on bubble CPAP. Bedside USG revealed mild ascites and pleural effusion B/L and there was RDS type of picture on chest X-ray. The baby was kept nil per oral and fluids were hiked. Considering mild rise in CRP value the antibiotics were further upgraded too and blood C/S was repeated. The child improved next day and CPAP was removed and over next 4 days remained clinically stable. On D8 of admission the baby had features of shock and was managed with fluid boluses and ionotropes. There was reappearance of fever (maximum recorded 100.6 °F). USG showed increased third space loss and chest X-ray was suggestive of right collapse consolidation. Dengue serology was sent and IgM dengue came positive. Baby started to have hemorrhagic manifestations, coagulation profile was abnormal (APTT 90, INR 1.73) and CRP shot up to 110 mg/L. Along with platelet, FFP transfusion was given and considering downhill course baby was put on mechanical ventilator. LFT on day 13 post-natal life showed elevated liver enzymes (SGOT 356/SGPT 565) and both blood culture reports were sterile. Echo was done twice to see myocardial function and was reported normal on both occasions. USG brain on day 16 of life showed diffuse brain edema. Inspite of using 3 ionotropes in moderate to high dosage (dopamine, dobutamine and noradrenaline) the mean BP was persistently below 40 mmHg. Inspite of all efforts baby sadly expired on day 16 of life.

3. Discussion/review of literature

DHF/DSS is uncommon in children below 1 year who are usually exposed to infection by dengue virus for the first time. However "infection-enhancing antibodies" acquired by the mother from previous Flavivirus infections are passively transmitted to the baby and this results in serious manifestations in the newborn.[7]

Maternal age was the only **risk factor** associated with dengue infection as older mothers (>20 years) were significantly more likely to be sero-positive than younger women. Cord antibody titers varied with maternal age and antibody titer were significantly higher in babies born to younger mothers (<20 years) and were significantly correlated with maternal titer. Low birth weight babies had Lower transfer ratios for antibody compared to heavier babies.[8] In our case mother's age was 29 years and possibly it was a secondary infection considering the severity in mother and the baby.

Although many arboviruses are known to cause fetal death, premature birth and teratogenic changes in humans and animals, the few reports of **fetal malformation or wastage from dengue infection** are poorly documented[6] and the evidence is contradictory. In case of early pregnancy, there is no evidence for vertical transmission[2] although there are reports of prematurity and low birth weight.[5]

The longer the time interval between the onset of maternal fever and delivery the sooner is the appearance of fever in the infant which is consistent with the incubation period of dengue infection of 5–7 days. The **incubation period** for dengue infection in infants or the duration between fever in mothers and infants, was shorter in mothers with secondary infection. Severe dengue occurs only when the clinical picture in the mother happens near term or the birth itself, and no time to maternal production of protective antibodies. In our case the fever in baby appeared on 8th post-natal day while mother had symptoms starting 5th post-natal day so it is quite probable that mother was infected quite close to the delivery day although infective period ranges 14 days before to 14 days after delivery. Theoretically horizontal transmission in our case report baby cannot be ruled out but considering the care in hospital it looks improbable.

Dengue serotypes may play a role in the severity of disease. Symptoms seemed to be more severe with secondary dengue type 2 infection.

The **mode of delivery** did not change the course of disease or reduce the rate of bleeding in infants.[9]

The dengue virus, an RNA virus, has a small molecular size (about 40–60 nm) and is concordant with the basic rule of **vertical transmission** in nanomedicine. Immunopathogenesis is proposed to be the main possible pathogenesis leading to congenital dengue infection. In the neonate with congenital dengue infection, the passed dengue virus from the mother might stimulate the antibody response and further induce thrombocytopenia via possible autoimmune mechanisms.

Three mechanisms of dengue-related illness in the fetus can be postulated[6]:

1. Maternal infection during pregnancy may result in hematogenous spread of the virus to the placenta and subsequent passage to the fetus.
2. Maternal viremia during labor could result in viral transmission and infection of the fetus or the newborn because of blood exchange during the delivery process.
3. Severe maternal illness during pregnancy or labor could alter placental function and injure the fetus in the absence of actual fetal infection.

Fever is the most common **Clinical feature** in congenital dengue infection. The age at presentation ranges from 16 h to 11 days after birth and lasts 2–6 days with body temperatures between 38.0 and 38.8 °C.[6] Biphasic fever was seen our case (fever reappeared on D 15 of life) and it has been reported once in newborns[10] but it is not a common feature. Fever in longer in children experiencing primary infections rather than secondary infection. Newborn infants often do not mount a febrile response to an infection, and consequently cases of perinatal dengue virus transmission may be missed if the mother is not identified as having dengue.[11] Similarly late appearance of fever may mimic late onset neonatal sepsis and confound the clinical picture. It is not uncommon to have raised CRP values as the disease advances as was seen in our case and reported in literature[12,13] Strong suspicion in an endemic zone is needed to diagnose congenital dengue infection. Non-specific signs such as poor sucking, irritability, diarrhea, and pallor may be present. Acrocyanosis or cyanosis of the perioral and periorbital area may be present for long duration. Hepatosplenomegaly with elevated enzymes (AST or ALT >1000) may herald onset of shock syndrome and should be interpreted as disease advancement and severe dengue.[14] Maculo papular Rash may be present on day 1 starting on face and spreading to involve the trunks and limbs later.

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