Clinical characteristics and viral kinetics of DENV-1 and DENV-4 congenital dengue in two newborns

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ABSTRACT

The cases reported the clinical characteristics and viral kinetics of DENV-1 and DENV-4 in two cases of congenital dengue. We describe two neonates born to mothers with recent dengue infections, highlighting their clinical presentation, serological progression and outcomes. Both neonates had early onset of symptoms, with one tested positive for DENV-4 and the other for DENV-1. Both experienced thrombocytopaenia without signs of haemoconcentration and recovered uneventfully. Congenital dengue, although rare, should be considered in neonates with fever and other suggestive symptoms in dengue-endemic areas. The two reported cases are unique in that both had congenital dengue fever with different serotypes, yet demonstrated prolonged NS1 antigen positivity and delayed seroconversion.

Key words congenital dengue; vertical transmission; neonate; DENV

INTRODUCTION

Dengue fever is the most common mosquito-borne viral infection globally, predominantly affecting populations in tropical and subtropical regions. However, congenital dengue remains underreported, as most national surveillance systems do not report vertical transmission of dengue explicitly. The incidence of vertical transmission varies widely in the literature, ranging from 1.6% to as high as 90%[1–3]. This wide range is likely due to inconsistencies in study methodologies, including variations in diagnostic tools, timing of assessments, and case definitions.

One of the largest cohorts was reported by Nguyen *et al*.[4] in Vietnam, describing 32 neonatal cases. Additional smaller series from Brazil[5], France[2], Mexico[6], and Paraguay[7] contribute another 25 cases, bringing the total described in literature to approximately 57 cases. These reports demonstrate significant heterogeneity in clinical and laboratory presentation across different geographic regions, including different rates of fever, respiratory distress, petechiae, and leucopoenia. While virological data is limited, it is noted that dengue virus serotype 2 (DENV -2) was the predominant strain in both the Mexican and Brazilian cohorts, the same groups that reported some of the lowest rates of fever and petechiae. The mortality rate was zero across most reported series, with the exception of one death in the Mexican case series.

While dengue fever commonly affecting adolescents and adults, rare cases of vertical transmission to neonates present distinct diagnostic and management challenges. Congenital dengue presents atypically in neonates, with clinical and serological features differing from the classical dengue. The classical dengue observed in older children and adults is characterised by headache, retro-orbital pain, myalgia, arthralgia, and bone pain. In neonates, these symptoms are either absent or cannot be assessed due to their inability to verbalise discomfort[8]. Instead, congenital dengue often presents as a non-specific febrile illness, with manifestations such as lethargy, poor feeding, respiratory distress, or a sepsis-like syndrome.

We report two cases of congenital dengue in neonates, describing the clinical presentations, serological progression and medical management. Both cases are notable for involving different serotypes (DENV-1 and DENV-4), yet shared a pattern of prolonged non-structural protein 1 (NS1) antigen positivity and delayed antibody seroconversion, suggesting unique viral kinetics in this age group.

Case history

Patient 1

A male neonate was delivered at 38 weeks' gestation via caesarean section due to an oblique lie during labour. The mother, a 27-year-old multiparous woman presented with fever and vomiting for two days prior to delivery. Laboratory results on admission showed leucopoenia and thrombocytopaenia. She was tested positive for both dengue NS1 antigen and immunoglobulin M (IgM), but negative for dengue immunoglobulin G (IgG), indicating an acute infection. A dengue serotyping test using quan-

titative reverse transcription polymerase chain reaction (qRT-PCR) was performed for the mother on day 10 of her illness, during the convalescent phase. However, the result was negative.

The neonate weighed 3.28 kg with APGAR scores of 9 and 10 at one and five minutes respectively. He was admitted to the special care nursery (SCN) for observation due to the risk of vertical dengue transmission. The neonate's initial dengue serology (NS1, IgM and IgG) was negative. Dengue serology was performed within the first 24 h of life despite the neonate being asymptomatic at birth, as the mother had dengue fever near the time of delivery, placing the neonate at high risk for congenital dengue. At 30 h of life, he developed signs of respiratory distress and required oxygen support. On day five, he developed fever, prompting a repeat of serological tests that returned positive for NS1 but remained negative for IgM and IgG. Dengue serotyping confirmed DENV-4 infection. By day seven, the neonate developed hepatomegaly and thrombocytopaenia. However, the neonate did not show any transaminitis or haemoconcentration throughout hospitalisation. His haematocrit levels did not exceed the initial readings of 53% at birth (Fig. 1). Serological markers showed NS1 remained positive until day 19 of life with IgM and IgG seroconversion occurred on day 9 and day 19 of life respectively (Fig. 2).

His fever subsided within four hours, and oxygen supplementation of stopped on the twelfth day. He did not require any intravenous fluids but received platelet transfusion due to severe thrombocytopaenia. An ultrasound cranium did not show any intraventricular haemorrhage. He was discharged well after a 15-day hospital stay. The neonate had an uneventful recovery and was started on breastfeeding on day 2 of life. As maternal lactation gradually increased, the neonate achieved full breastfeeding by day 7 of life.

Patient 2

A female neonate was delivered at 38 weeks via emergency caesarean section due to foetal distress. Her 30-year-old mother, para 2, had experienced fever without any other accompanying symptoms a day before delivery. The mother was noted to have leucopoenia and tested positive for Dengue NS1 antigen on admission.

The neonate weighed 2.95 kg and had similar APGAR score as patient 1. She was admitted to the SCN post-delivery due to the risk of congenital dengue. She remained asymptomatic until day 5 when she developed fever, jitteriness and macular rashes over the abdomen. Dengue test revealed positive NS1 antigen but negative IgM and IgG. Dengue serotyping confirmed DENV-1 infection in both mother and child.

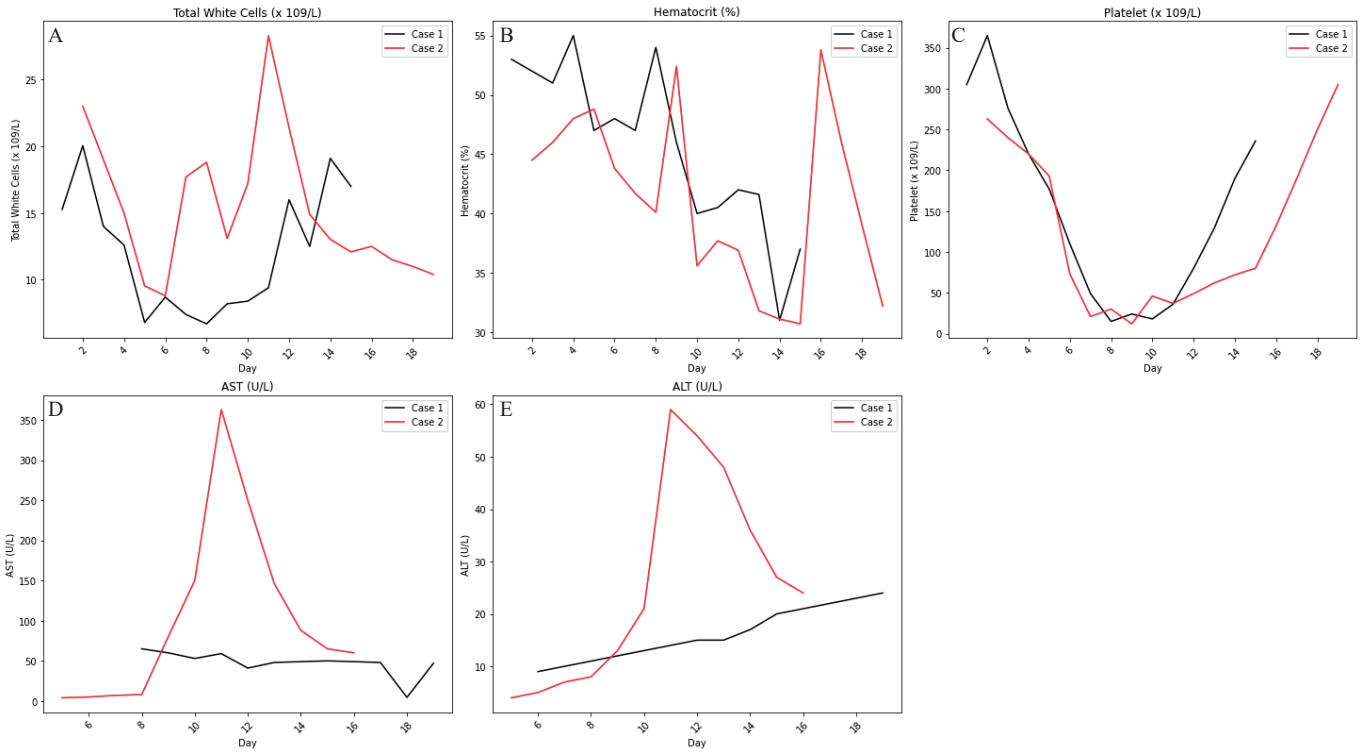

Fig. 1: Serial laboratory parameter trends over time in two cases of congenital dengue. Each panel (A-E) illustrates the temporal trends for key blood parameters, including: A. Total White Cells, B. Hematocrit, C. Platelet count, D. AST and E. ALT.

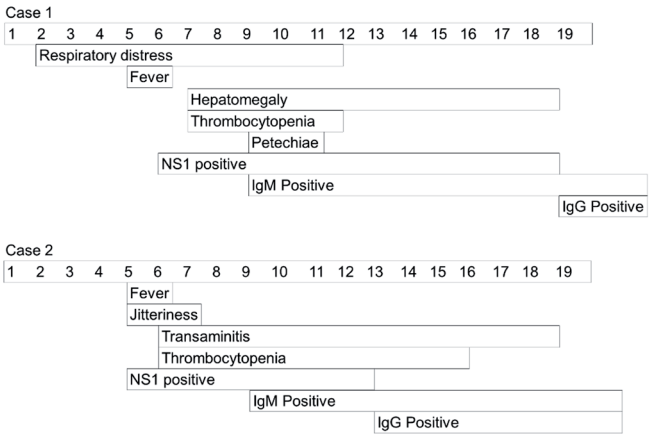

Fig. 2: Timeline of clinical manifestations and serological markers in two cases of congenital dengue.

Her clinical symptoms were transient, with fever lasting around 20 h and the jitteriness and rashes resolved the same day. However, she developed thrombocytopaenia and transaminitis the following day. Thrombocytopaenia normalised by day 16 of life. Haemoconcentration was not observed in serial full blood counts (Fig. 1). Transaminitis peaked on day 11 with significantly elevated aspartate aminotransferase (AST) levels compared to alanine aminotransferase (ALT). Chest radiograph showed no signs of myocarditis. NS1 remained positive until day 13, with IgM and IgG seroconversion on day 9 and day 13, respectively (Fig. 2).

The neonate remained haemodynamically stable throughout the hospitalisation and was exclusively breastfed from day 6 of life onward. She did not require any intravenous fluid or oxygen therapy but received platelet transfusions for severe thrombocytopaenia. An ultrasound cranium was normal, and she was discharged well after a 15-day hospital stay.

DISCUSSION

Congenital dengue is uncommon and typically occurs when maternal infection is acquired near delivery before protective antibodies can be transferred to the neonate[9]. Clinical manifestations of congenital dengue generally appear within the first week of life, with affected neonates exhibiting fever, respiratory distress, rash, hepatomegaly and transaminitis.

We report two cases with differing symptoms, born to mothers with acute dengue infection. Patient 1 presented with respiratory distress despite an initial negative NS1 antigen test. This could be attributed to low level of viraemia below the detection threshold of qualitative antigen testing, which might have been detected if qRT-PCR had been performed at birth. Later on, the onset of fever on day five of life coincided with NS1 positivity, signifying active viraemia. Patient 2 showed no respiratory symptoms but developed fever, jitteriness and transaminitis by day five. Both neonates in this report presented with fever. While fever is a common feature of dengue in older children, its frequency in congenital dengue is highly variable, reported in 20% to 100% of cases across studies[4-6, 10]. This variability may reflect differences in immune maturity, viraemia levels, or the protective effect of maternal antibodies. The brief duration of fever in patient 1 is not unusual, as dengue can present across a wide clinical spectrum, from transient febrile responses to prolonged fever. Next, elevated liver enzymes are observed in 25% to 33% of neonates with congenital dengue[5, 10]. Both our patients and a Vietnamese cohort showed predominant AST elevation over ALT. This pattern may reflect a systemic inflammatory response or involvement of non-hepatic tissue rich in AST, such as cardiac and skeletal muscle.

Young neonates are predisposed for severe dengue infections due to their immature immune system. The waning of maternal antibodies can lead to more severe outcomes through antibody-dependent enhancement (ADE)[11–12]. ADE occurs when non-neutralizing antibodies facilitate the entry of dengue virus into the cells and replicate more easily, potentially worsening the severity. This mechanism is particularly relevant in infants born to mothers with recent dengue infection, as maternal antibodies may decline over time and become sub-neutralizing, increasing the infant's risk for severe disease. However, the two neonates described had mild illness without signs of haemoconcentration. In neonates, absolute haematocrit values are not a reliable parameter of plasma leakage due to their naturally higher haematocrit values after delivery[13]. Instead, a more reliable indicator of plasma leakage is an increase from baseline haematocrit of more than 20%[8], which was not observed in both patients. In our report, the mild clinical course is unlikely due to maternal antibody protection since the infants had absence of detectable IgG at birth. Instead, it may reflect an attenuated response due to the neonate's immunological immaturity. The mild course of illness aligns with other reports of congenital dengue[5, 10, 14], suggesting distinct pathophysiology from dengue in older infants, where waning maternal antibodies can predispose to severe disease through ADE.

Treatment for dengue is primarily supportive and the transfusion of platelets are generally not recommended in dengue infections. However, there are reported cases in literature where platelet transfusions have been given[15–17], despite the controversy surrounding this practice. This was likely considered due to the risk of intraventricular haem-

orrhage in neonates, with thrombocytopaenia recognised as a risk factor for intraventricular haemorrhage[18]. Both our patients received platelet transfusions to mitigate the risk of intraventricular haemorrhage after careful consideration of the benefits and risks of the transfusion.

In addition to supportive care, breastfeeding in the context of maternal dengue infection warrants further discussion. Dengue viral RNA can be detected in breast milk during maternal viraemia[19–20], leading to postulation on breastfeeding as a potential route of transmission, although postnatal transmission via breast milk has not been definitely established. However, the benefits of breastfeeding are widely considered to outweigh this theoretical risk, and major public health authorities, including the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organisation (WHO), continue to recommend breastfeeding even in mothers with dengue. In this report, patient 1 developed fever on day 5 of life and was partially breastfed at that time. Given the incubation period and clinical timeline, transplacental transmission remains the more likely route of infection.

The typical serological progression of dengue infection includes positivity of the NS1 antigen in the first week of illness and emergence of IgM antibodies around day 3 to 5[8]. However, the serological kinetics in neonates with congenital dengue could differ. Notably, in our patients, there was prolonged antigenaemia up to day 19 of life. The persistence of NS1 antigen beyond the usual window may be explained by immature neonatal clearance mechanisms or delayed immune activation. Prolonged NS1 positivity has also been reported in immunocompromised individuals[21], suggesting a link between immune maturity and antigen clearance. Additionally, both neonates demonstrated IgM seroconversion by day 9, with subsequent IgG seroconversion occurring between day 13 and day 19. This indicates a delayed immune response in neonates compared to older populations.

Several limitations must be acknowledged. First, the small sample size limits generalisability of the findings. Second, the absence of viral load quantification hinders the ability to correlate clinical outcomes with the viral load. In addition, the lack of long-term follow-up precludes evaluation of long-term clinical outcomes. Future larger cohorts that perform quantitative virological assessments, and longitudinal monitoring are needed to build upon these findings and address these gaps.

CONCLUSION

Our report highlights the importance of considering dengue in the differential diagnosis for neonates presenting with fever and thrombocytopaenia in endemic areas. The prolonged NS1 positivity and delayed seroconversion illustrate the unique serological kinetics of dengue in neonates. Lastly, the availability of serotyping results in our patients further adds uniqueness to our report.

KEY MESSAGE

Consider congenital dengue as a differential diagnosis for neonates with fever in endemic regions. Prolonged NS1 antigenaemia and delayed antibody seroconversion occurred in these neonates highlight the unique viral kinetics and immune responses compared to older populations.

Ethical statement

This case report was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the patients' legal guardians for the publication of clinical information and medical data. Patient confidentiality and anonymity were strictly maintained throughout the preparation of this manuscript, and all identifying information has been omitted to protect patient privacy.

Conflict of interest: None

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