Case Report: Chikungunya and Neonatal Immunity: Fatal Vertically Transmitted Chikungunya Infection

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Abstract. Chikungunya is a mosquito-borne infectious disease that has emerged as a global pathogen. The virus can pass vertically from mother to child especially during the perinatal period, with an intrapartum vertical transmission rate of 50%. Approximately half of the neonates infected with chikungunya present with severe symptoms and infrequently death. This report summarizes two severe cases of vertically transmitted neonatal chikungunya infection. One case was confirmed by real-time reverse transcription polymerase chain reaction and the other fulfilled clinical and epidemiological criteria. Both infants presented on day 3 with abdominal distension, reduced perfusion pressure, and hypotension; acrocyanosis progressing to ischemic digits; and respiratory distress. Both died within 24–48 hours of presentation. The severity of symptoms observed is likely due to a combination of contamination of the fetal blood from highly viremic mothers during delivery and a low innate antiviral type-1 interferon response. Further examination of the neonate's innate immune response to chikungunya may provide clues for the development of potential treatment or vaccine interventions.

INTRODUCTION

Chikungunya is an arboviral infectious disease that has emerged as a truly global pathogen infecting millions in over 50 countries.¹ It is transmitted to humans by the *Aedes aegypti* and *Aedes albopictus* mosquitoes, and can pass vertically from mother to child especially during the perinatal period. Neonates are more likely to be affected the closer to term the mother contracts the infection and can present with severe multiorgan involvement and, infrequently, death.^{2–4} The pathogenesis is uncertain; however, the severity of infection is thought to be related to a high maternal viral load exposure at delivery.

We report two cases of vertically transmitted chikungunya in neonates associated with severe disease and death during the 2014 chikungunya outbreak in Jamaica and review early life immunity to chikungunya infection.

CASE 1

A 35-week, 2-kg male with Apgar scores of 4¹, 6⁵, 7¹⁰ was born via emergency cesarean section to a gravida-4 mother with negative serology for syphilis and human immunodeficiency virus (HIV). The mother was admitted with a 1-day history of fever and joint and abdominal pain. She was evaluated for sepsis, pyelonephritis, and chikungunya. An abnormal nonstress test and cardiotocography prompted an emergency cesarean section on day 2 of admission. The mother subsequently developed thrombocytopenia, leukocytosis, disseminated intravascular coagulation, and acute renal failure secondary to rhabdomyolysis. She died on day 4 post-delivery. Real-time reverse transcription polymerase chain reaction (RT-PCR) was positive for chikungunya. Dengue titers and blood and urine cultures were all negative.

On admission to the nursery postdelivery, the infant was noted to have mild respiratory distress on examination. Lung fields were clear and there was no cardiac murmur.

He was admitted to the special care nursery with a differential diagnosis of respiratory distress syndrome, transient tachypnea of the newborn, presumed sepsis, and congenital chikungunya. Blood, urine, and cerebrospinal fluid (CSF) cultures and complete blood count were requested. He was commenced empirically on ampicillin and gentamycin, given oxygen via a head box at 5 L/minute and 10% dextrose water intravenous fluids. His respiratory status improved within 24 hours and he was subsequently weaned off oxygen, and formula feeds were then commenced. His septic screen was negative, and urea electrolytes and bilirubin were within normal limits on day 2 of life.

On day 3, he was noted to have both cyanosis and apnea with a low oxygen saturation of 76%. He had acrocyanosis of the toes of both feet. Examination of vital signs at the time recorded a temperature of 99.8°F, a pulse rate of 132/minute, and a blood pressure of 56/27 mmHg, which was below normal for age. He was lethargic and had mild abdominal distension and a coffee-ground aspirate. His random blood sugar at this time was 0.6 mmol/L (normal 2.8–8.3 mmol/L). He received supplemental oxygen, intravenous fluid resuscitation, and antibiotics were switched to ceftazidime and amikacin. His repeat complete blood count at the time of deterioration was normal (Hb 14.3 g/dL, white blood cell [WBC] 7.1×10^9 /L, platelet 202×10^9 /L). Blood, urine, CSF, chest and abdominal radiographs were all unremarkable with no evidence of necrotizing enterocolitis. On day 4, his acrocyanosis involved both hands and feet and his toes started exhibiting ischemic changes at the tips. He had reduced peripheral perfusion evidenced by decreased pulse pressure and capillary refill of 10 seconds. He became febrile with a temperature of 101°F. His oxygen saturation decreased to 50% and increased to 98% on 5 L of oxygen via face mask. The abdominal distension worsened with progress to type-1 rectal prolapse. Differential diagnoses at this stage included septic shock and vasculitis with limb ischemia. The infant received fluid and plasma infusions, stress doses of hydrocortisone (3 mg/kg), intravenous immunoglobulin, and meropenem. He was then placed on continuous pulmonary airway pressure. Despite resuscitative efforts, the infant rapidly deteriorated and died on day 4 of life.

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The RT-PCR for chikungunya collected on day 1 of life was positive. A post mortem examination was not conducted.

CASE 2

A 38-week, 2.9-kg male was born via spontaneous vaginal delivery with Apgar scores 7¹, 9⁵, a week after case 1, to a primigravida with negative serology for HIV and syphilis. The mother presented with fever and joint pains on the day of delivery. The fever abated on day 2 postdelivery and her joint pains resolved. The neonate presented on day 3 of life with fever, lethargy, feeding poorly at the breast, and a rash. Clinically, he was mildly dehydrated, had a generalized maculopapular rash, lethargy, and a temperature of 101.8°F. He was assessed for septicemia and congenital chikungunya, and was commenced on penicillin and gentamycin. Complete blood count, urea, and electrolytes were all normal for age, and the blood, urine, and CSF screens were sterile. At day 4 of life, the infant began displaying progressive abdominal distension and respiratory distress. His blood pressure fell to 44/16 mmHg (normal 90/50 mmHg), his right foot digits became cyanosed, his pulse pressures fell, and he became anasarctic and anuric. This prompted ventilator support and a switch of antibiotics to ceftazidime and amikacin.

Pathology examination revealed a bicytopenia (Hb 9.3 g/dL, WBC $4.1 \times 10^9/L$, platelets $96 \times 10^9/L$), electrolyte imbalance, renal impairment (sodium 118 mmol/L, potassium 8.5 mmol/L, chloride 91 mmol/L, bicarbonate 13 mmol/L, urea 9.3 mmol/L, creatinine 97 $\mu\text{mol/L}$), and deranged liver function tests (total bilirubin 51 IU/L, direct 18 IU/L, aspartate aminotransferase (AST) 707 IU/L, and alanine aminotransferase 118 IU/L).

Abdominal radiograph showed dilated loops of bowel with no evidence of necrotizing enterocolitis. Despite resuscitative measures, including provision of stress doses of hydrocortisone, the infant died on day 4 of admission, at 1 week of life. The chikungunya samples were not processed due to the large numbers submitted to the laboratory at the peak of the epidemic.

DISCUSSION

Both mothers described in this case report had clinical features of chikungunya within 2 days preceding delivery, with different maternal outcomes and similar neonatal outcomes. The mother of case 1 had renal impairment complicated by rhabdomyolysis, whereas the mother of case 2 described a benign course. Both infants manifested symptoms on day 3 of life and described a similar natural history of reduced perfusion pressures, acrocyanosis progressing to ischemic digits, abdominal distension, respiratory distress, and death. The mother of the second case fulfilled clinical and epidemiological criteria for chikungunya⁵ but was not confirmed by formal laboratory studies. Both cases were epidemiologically associated in both time and geography.

During intrapartum viremia, the vertical transmission rate of chikungunya is reported as 48.7%. Mothers who have a high viral load in their placenta are more likely to transmit the virus.² In the infected newborns, symptoms generally develop on days 3–7 of life with fever, rash, and peripheral edema. Pathology typically reveals a bicytopenia, increased prothrombin time, and AST, which were manifested in

case 2. The presentation is subsequently complicated by seizures, hemorrhagic syndrome, hemodynamic disorders, displayed by both infants, and myocardial dysfunction.^{2–4}

Furthermore, acrocyanosis was documented in both cases. Acrocyanosis has previously been described in 75% of 56 chikungunya-infected infants less than 1 year of age without hemodynamic instability,⁶ and has not been documented in older children.⁷ In a small number of adults, transitory peripheral vascular disease such as Raynaud's phenomenon lasts for several weeks during the second and third month after infection,⁸ which may be due to immune-mediated endothelial damage.⁹ A normal white cell count and sterile cultures were inconsistent with an inflammatory or septic picture and steroids and antibiotics were not useful in either case and have not been shown to be of benefit.⁵ The abdominal distension and ischemic digits may have been due to hypoperfusion. Studies of vertical transmission of chikungunya in mouse models suggest that the placental tissue itself is not infected by virus.¹⁰ It is postulated instead that free virus particles from the highly viremic mother contaminates fetal blood through placental breaches during labor.² The virus, directly inoculated in the fetal blood stream, bypasses the usual route from dermis to the lymphatic system and disseminates in the blood circulatory system to target organs where viral replication continues.¹¹

In the pathogenesis of chikungunya infection, interferon plays a critical role in preventing viral replication in the early stages of disease. Mouse models demonstrate that chikungunya disease severity is associated with a defect of type-1 interferon signaling that occurred in neonatal mice.¹ Human neonates have been shown to have low levels of toll-like receptor-induced interferon production.^{12,13} A high maternal viral load, chikungunya tropism for specific target organs and neonatal host factors such as the relative proportion of tissue fibroblasts, and the rate of cell division¹¹ along with immune ontogeny of the neonatal immune system compared with adults¹² may contribute to disease severity. Further examination of the neonate's innate immune response to chikungunya may provide clues to potential treatment and/or vaccine interventions.

Received June 16, 2016. Accepted for publication January 14, 2017.

Published online February 6, 2017.

Acknowledgment: I would like to acknowledge J. Peter Figueroa, Professor of Public Health and Epidemiology at the University of the West Indies for his encouragement in the preparation of the manuscript.

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