Congenital and Neonatal Chikungunya in Colombia

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Received October 5, 2015; accepted March 19, 2016; electronically published April 28, 2016.

In Latin America and the Caribbean (LAC), chikungunya (CHIK) viral infection has emerged as a significant arboviral disease. This rapidly expanding vector-borne viral illness is associated with a substantial burden of disease in terms of acute illness and also in terms of long-term sequelae. In addition, this viral pathogen has the ability to impact different populations including pregnant women and newborns. Despite the growing threat of this arboviral infection to the region, there are insufficient reports or studies attempting to delineate the clinical and epidemiological features of congenital and neonatal cases of CHIK in LAC. In this study, we present a case of congenital CHIK and a case of neonatal CHIK infection identified in Santander, Colombia. We discuss the potential neurological impact and sequelae of CHIK infection acquired during the neonatal period. There is an urgent need for further epidemiological and clinical studies to better understand the impact of CHIK in endemic areas in LAC.

Key words. chikungunya; Colombia; congenital; Latin America; neonatal.

Between the end of 2013 and January 2016, more than 2 million cases of chikungunya (CHIK) infection have been reported in many urban and rural settings in Latin America and the Caribbean region (LAC) [1, 2]. Chikungunya infection affects mostly adult populations, but it may also produce illness among pregnant women and children. Furthermore, congenital cases have been described, and children of any age may also develop symptomatic illness, sometimes leading to devastating consequences [3, 4]. Despite the recognized burden of disease associated with CHIK infection in the ongoing epidemic in LAC, there is little information regarding the clinical and epidemiological features of this infection. In particular, much remains to be elucidated regarding transmission dynamics, clinical manifestations, and overall public health impact of congenital and neonatal CHIK infection.

Colombia has been one of the most CHIK-stricken countries in Latin America with over 480 000 reported cases between August 2014 and February 2016. In particular, there have been an increasing number of reported cases of CHIK infection in Santander, with more than 10 000 cases (>95% occurring during 2015) affecting different age groups. Therefore, we need to understand the medical impact of CHIK infection in children, including the spectrum of clinical manifestations, and its potential long-term complications. However, there are only a limited number of studies being conducted in Colombia and elsewhere in LAC to better delineate the impact of CHIK infection in the pediatric population, including cases of congenital CHIK infection [3–6].

There is only 1 recent report of congenital CHIK infection from Latin America. In this study, 8 cases of congenital CHIK infection were described with 3 associated deaths [4]. It is interesting to note that although all 8 cases were considered to have severe disease, none of them were considered to have neurological complications [7]. There are some case reports of neurological affection occurring in congenital and neonatal cases of CHIK infection. The incidence of neurologic complications associated with CHIK infection is low among adults described in different settings in Latin America [8].

Our understanding of the transmission dynamics and clinical phenotypes of congenital CHIK transmission and its clinical implications needs to be further elucidated.

Journal of the Pediatric Infectious Diseases Society, Vol. 5, No. 3, pp. e17–e20, 2016. DOI:10.1093/jpids/piw021

Therefore, we need to better understand the transmission dynamics, clinical phenotypes, and long-term sequelae of CHIK infection in neonates infected congenitally, or those with CHIK infection acquired during the neonatal period. We present 2 illustrative cases of CHIK infection, 1 congenital case and 1 neonatal case of infection, to illustrate the potential neurological impact of CHIK infection in this particular age group.

CASE DESCRIPTIONS

Case 1

A 1-year-old newborn female born by cesarean section, from a mother that 1-day before delivery developed fever, edema, pelvic pain, and a maculopapular exanthem (no serology for CHIK was obtained). She weighed 2800 grams at birth, which occurred at 38 weeks of gestation. Three days after birth, the newborn developed fever (38.5°C), which lasted for 74 hours (oscillating between 37.5°C and 38.5°C). Approximately, 24 hours after the fever subsided, an erythematous maculopapular exanthem was identified in her trunk along with jaundice, distal cyanosis, and extreme irritability. A lumbar puncture was performed demonstrating no evidence of pleocytosis, and Gram stain and cultures of cerebrospinal fluid were reported as negative. An ultrasound of the brain was performed and there was no evidence of abnormalities. Due to a clinical suspicion of neonatal sepsis, the newborn was transferred to our institution in Santander, Colombia. During admission, she was found to have a respiratory rate of 42 breaths per minute and a heart rate of 120 beats per minute. While receiving oxygen at 1 liter per minute via nasal cannula, her SpO_2 was 99%. Her laboratory test demonstrated evidence of thrombocytopenia (112 000/μL), a total bilirubin level of 15.2 mg/dL (indirect bilirubin of 14.8), alanine aminotransferase of 16 μ/L, aspartate aminotransferase of 74 μ/L, and C-reactive protein value of 7.03 mg/L. Ultrasonography of her heart and abdomen demonstrated no abnormalities. Blood and urine cultures were obtained, all of them reported negative; there was also no serological or clinical evidence of TORCH infections. Due to the ongoing outbreak of CHIK infection in the area and a lack of alternative diagnosis, samples for serological assessment of CHIK were obtained. The diagnosis was confirmed by an immunoglobulin (Ig)M enzyme-linked immunosorbent assay (ELISA) test, which was performed at the Arbovirus Laboratory, Virology Group, National Institute of Health, Bogotá, Colombia. Other viral serologies were obtained including dengue serology (IgM ELISA test), which was reported as negative. She was treated initially with acetaminophen (15 mg/kg per dose, q6 h), intravenous (IV) hydration (120–150 mL/kg per day), ampicillin, and gentamicin for 3 days. All of these interventions were discontinued once the diagnosis of CHIK was confirmed. She was hospitalized for 9 days, and fever and jaundice gradually subsided within a period of 5 days. After her discharge, she has been closely observed over a period of 12 months, and her psychomotor development has been reported as normal.

Case 2

A 20-day-old male newborn male, delivered vaginally (weighed 3700 grams at 39 weeks of gestation), was taken to a local pediatrician for evaluation 23 days after birth. The infant presented with a history of fever that lasted for 4 days (38.5°C). By the time the fever subsided, a diffuse maculopapular rash was identified and associated with the patient's profound irritability, which persisted for approximately 3 days. On skin examination, there was no evidence of lesions consistent with mosquito bites. The newborn was referred to our institution in Santander, Colombia after developing generalized seizures, cardiopulmonary compromise, and stupor. His admission laboratory tests demonstrated severe thrombocytopenia (40 000/μL) and lymphopenia (770/μL, 8.9% of white blood cell counts). During his hospital stay, his mother and grandmother were diagnosed with CHIK infection clinically and by serologic confirmation. A lumbar puncture was performed showing >5 cell/mm^3 with mononuclear predominance, red blood cell counts of 1/mm^3, protein level of 102 mg/L, and a glucose level of 35 mg/dL (45% of serum level). Blood, urine, and cerebrospinal cultures were negative. In addition, latex agglutination test for detection of *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* were nonreactive. An abdominal ultrasound was performed and reported as normal. A magnetic resonance imaging (MRI) of the brain was performed and showed signs of restricted diffusion in periventricular white matter and corpus callosum (Figure 1). Axial T2-weighted imaging shows symmetrical hyperintensity of the periventricular white matter, and gradient echo T2* revealed small hypointense foci of microhemorrhages at the head of the right caudate nucleus (Figure 1). The combination of these findings was consistent with encephalitis due to CHIK infection. The diagnosis of CHIK was confirmed by serological testing IgM ELISA performed at the Arbovirus Laboratory, Virology Group, National Institute of Health, Bogotá, Colombia. In addition, dengue serology was performed (IgM ELISA test), which was negative, and there were no serological or clinical manifestations of TORCH agents. The patient was treated initially with acetaminophen (15 mg/kg per dose every 6 hours) and IV hydration (150 mL/kg per day). Clinical symptoms gradually subsided within 14 days. The patient is still under observation. Thirteen months after infection, the patients has mild auditory impairment, with altered auditory-evoked

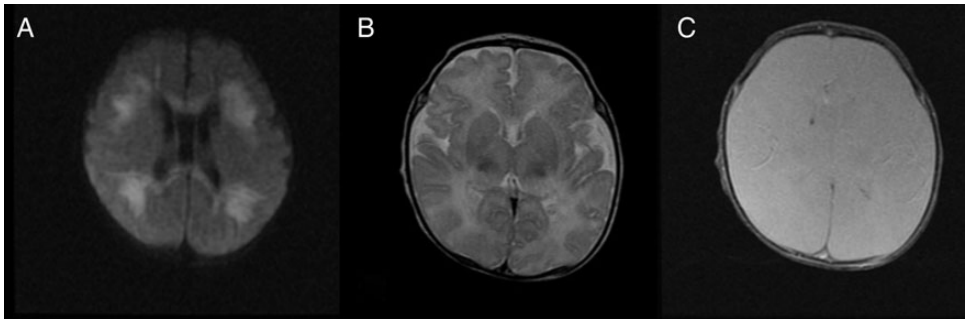

Figure 1. (A) Magnetic resonance images of the brain demonstrating suggestive findings consistent with Chikungunya encephalitis. Diffusion weighted imaging shows restricted diffusion in the periventricular white matter and corpus callosum. Axial T2WI demonstrates symmetrical hyperintensity of the periventricular white matter (B) with hypointense foci of microhemorrhages at the head of the right caudate nucleus in gradient echo T2* image (C).

potentials. There is also evidence of decreased muscle tone associated with delays in sitting with no support, crawling, and walking.

Of note, when these cases were evaluated at our institution, there was no evidence of circulating Zika virus and human infection in Santander, Colombia (both cases were seen and attended before September 2015).

DISCUSSION

Given the ongoing large epidemics of CHIK infection in LAC, it is crucial to delineate the epidemiology, clinical manifestations, and long-term impact of this arboviral infection among highly affected populations. In children, the clinical spectrum of acute CHIK infection and its associated long-term sequelae require further assessments. In particular, currently available information regarding the clinical spectrum and long-term outcomes of central nervous system (CNS) manifestations is limited.

Acute CHIK infection with affection of the CNS associated with neuroimaging abnormalities has been previously demonstrated in the children [3, 7–9]. In fact, cases of encephalitis and febrile seizures in the pediatric population have been reported with unremarkable or mild abnormalities in cerebrospinal fluid findings but with abnormalities identified in MRI [9]. We believe that the most concerning findings stemming from these reports is the occurrence of long-term sequelae. In some cases, neurologic sequelae were described at 6 months of follow up [9], but sequelae were still present 2 years after the acute episode of CHIK encephalitis [10]. Based on these findings, there is a need for close, long-term follow-up and neurological reassessments of neonates identified with CHIK infection, particularly those with congenital infection. The case fatality rate in congenital CHIK infection is reported to be 0.8% to 37.5% [4, 5, 11]. Fortunately, both of our cases survived.

Based on the timing of clinical manifestations and the prevailing outbreak of CHIK in the community where this baby was born, CHIK infection was likely acquired in utero in our first case. This is further supported by the fact that the usual incubation period of CHIK infection is 3–7 days (range, 3–12 days). Chikungunya infection in our second case was classified as neonatal acquisition, because the patient presented with clinical manifestations occurring during his fourth week of life, and at the same time that his mother and grandmother were confirmed to have CHIK infection. It is interesting to note that, as observed in previous reports [4], a cesarean section does not prevent transmission of CHIK (see Case 1).

Optimal supportive treatment should consider the high clinical variability of the disease progression in congenital and in neonatal cases that ranges from asymptomatic cases to febrile exanthematic and limited clinical acute phase to multisystem severe life-threating conditions. Central nervous system manifestations include meningoencephalitis, myelitis, and other neurological complications, which can even lead to death, as has been reported in congenital cases in Colombia [4]. In highly endemic zones, the risk of vector-borne cases in newborns and infants is considerable. Unfortunately, several gaps in our knowledge of CHIK-related CNS disorders still need to be addressed, ie, the limited availability of histopathologic assessments and detailed imagining studies of CHIK-associated CNS disease. Nevertheless, pediatricians should be aware that neurological sequelae can occur, especially in infants (with particular regard to the neonatal period) [4, 9, 10, 12]. Long-term follow up (minimum of 2 years) is required for confirmed cases of CHIK infection acquired congenitally or during the neonatal period to assess long-term sequelae from a neurologic and psychomotor perspective.

Regarding the diagnostic confirmation of CHIK infection, it should be noted that IgM cross-reactivity of human CHIK virus infections cases with other alphaviruses remains an important consideration in settings where there is concomitant circulation of other arboviruses. Fortunately, there is no evidence of cocirculation of other alphaviruses in Colombia, particularly in this region

at this time (ie, Mayaro, Eastern Equine Encephalitis or Venezuelan Equine Encephalitis). It is important to mention that laboratory workup should include both IgM and nucleic acid amplification testing; however, this last test was not done in our cases, which represents a limitation of our report. Furthermore, the detection of IgM for DENV does not necessarily rule out an infection by CHIK, and coinfections may occur.

CONCLUSIONS

Our descriptions of the clinical impact of CHIK infection in neonates with congenital or neonatal infection reveal the public health relevance of this arboviral infection. Therefore, it is crucial that further clinical and epidemiological studies are conducted in Latin America to design and implement appropriate public health interventions. Chikungunya has transitioned from an epidemic pattern to an endemic one in many urban and rural settings in the region, and it has been expanding rapidly [1, 4]. Thus, countries in LAC need to continue to monitor the epidemiology and long-term clinical sequelae associated with CHIK infection.

Acknowledgments

We thank Diane Edrington and John Gipson (Tulane University) for their English review of the manuscript.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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