

Mother-to-child Chikungunya Virus Transmission in Mae Sot District, Tak Province, Thailand 2019

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บทคัดย่อ: การติดเชื้อไวรัสชิคุนกุนยาจากมารดาสู่ทารกแรกเกิดในอำเภอแม่สอด จังหวัดตาก พ.ศ. 2562

รุ่งรัตน์ สุขารมย์ พ.บ.

กลุ่มงานกุมารเวชกรรม โรงพยาบาลแม่สอด ตำบลแม่สอด อำเภอแม่สอด จังหวัดตาก 63110

Background: Based on the epidemiological data of the Department of Disease Control (DDC), Ministry of Public Health (MOPH), outbreaks of chikungunya fever were reported in Thailand in 2019. Tak Province was one of the four affected provinces. Morbidity rate in the province was 138.39 per 100,000 populations. Mae Sot District, Tak Province, was one of the districts where there were suspected cases of chikungunya virus infection, whose signs and symptoms typically included fever, joint pain, and rash. This patient population also included pregnant women who had signs of chikungunya fever around the time of birth. Chikungunya virus could have been transmitted from mothers to their children as it was found that some newborns had shown similar signs (fever, rash, swelling) to those of their mothers within the first week of life. **Objective:** To study clinical signs and symptoms of chikungunya fever in neonates, clinical complications, and laboratory findings. **Method:** A descriptive study was conducted to monitor and observe signs, symptoms and laboratory findings of newborns who contracted chikungunya virus from their mothers, who had clinical signs within one week before delivery. Data were collected from June to October 2019, at Mae Sot General Hospital, Mae Sot District, Tak Province. Both newborns and mothers had blood samples collected and confirmatory laboratory testing was performed using chikungunya IgM antibody assay and/or chikungunya polymerase chain reaction (PCR) technique. **Result:** Six pregnant women developed fever, joint pain, and rash prior to delivery, 83% had positive IgM. All neonates born from six mothers developed fever and maculopapular rash. Signs and symptoms observed in up to 5 newborns (83.3%) included diffuse, limbs edema, irritability, respiratory distress and hyperpigmentation. Other signs and symptoms included poor feeding (50%), seizure and clinical encephalitis (33.3%) and hemodynamic instability (16.7%). Abnormal laboratory findings were observed. Six newborns had positive IgM and three had positive PCR. Two newborns developed encephalitis. No fatal outcomes. **Conclusion:** Chikungunya virus can be vertically transmitted from the mother to her child during pregnancy. Affected newborns may develop sepsis-like illness. Vertical transmission of chikungunya can lead to severe complications, particularly neurological involvement. It is important to consider chikungunya as differential diagnosis in newborns with sepsis and, or encephalitis in the outbreaks areas.

Keywords: Chikungunya, Newborn, Vertical transmission, Sepsis-like illness

บทคัดย่อ

ภูมิหลัง: จากข้อมูลทางระบาดวิทยาของกรมควบคุมโรค กระทรวงสาธารณสุข พบการระบาดของโรคไข้ปวดข้อชิคุนกุนยาในประเทศไทยในปี พ.ศ. 2562 จังหวัดตากเป็น 1 ใน 4 จังหวัดที่พบอัตราป่วย 138.39 ต่อแสนประชากร อำเภอแม่สอด จังหวัด

ตากเป็นหนึ่งในอำเภอที่พบการรายงานว่ามีผู้ป่วยแสดงอาการไข้ปวดข้อ ออกผื่น สงสัยโรคชิคุนกุนยา เป็นจำนวนมากรวมทั้งหญิงตั้งครรภ์ที่มีอาการแสดงในช่วงใกล้คลอดและสามารถถ่ายทอดเชื้อไวรัสชิคุนกุนยามาสู่ทารกได้ ทำให้ทารกแรกเกิดมีอาการแสดงไข้ผื่น บวม ตามมาภายในช่วงอายุ 1 สัปดาห์หลังคลอดคล้ายคลึง

กับมารดา **วัตถุประสงค์:** เพื่อศึกษาข้อมูลลักษณะอาการ อาการแสดงของโรคชิคุงุนยาในทารกแรกเกิด ภาวะแทรกซ้อนและผลทางห้องปฏิบัติการที่ตรวจพบ **วิธีการ:** เป็นการศึกษาเชิงพรรณนา (descriptive study) ติดตามลักษณะอาการ อาการแสดงและผลทางห้องปฏิบัติการของทารกแรกเกิดที่ติดเชื้อไวรัสชิคุงุนยาจากมารดาที่มีอาการแสดงในช่วง 1 สัปดาห์ก่อนคลอด เก็บข้อมูลในช่วงเดือนมิถุนายน-ตุลาคม ปี พ.ศ. 2562 โรงพยาบาลแม่สอด อำเภอแม่สอด จังหวัดตากผู้ป่วยทารกแรกเกิดมีอาการแสดงในช่วงอายุ 1 สัปดาห์หลังคลอด ทั้งทารกและมารดามีการตรวจเลือดยืนยันด้วย chikungunya IgM antibody และ, หรือ chikungunya polymerase chain reaction (PCR) **ผล:** จากการศึกษาพบมารดาทั้ง 6 ราย มีอาการแสดงไข้ ปวดข้อ ออกผื่น ในช่วง 1-2 วันก่อนคลอด มีการตรวจยืนยันด้วย chikungunya IgM ให้ผล บวก ร้อยละ 83 อาการแสดงของทารกทุกรายที่สำคัญ คือ ไข้ และผื่นแดงผู้ป่วย 5 ราย (83.3%) มีอาการบวม, กระสับกระส่าย, หายใจเหนื่อย, ผื่นรอยดำ, พบผู้ป่วย 3 ราย (50%) กินได้น้อย 2 ราย (33.3%) มีอาการชัก และ 1 ราย (16.7%) มีระบบไหลเวียนโลหิตไม่คงที่ผลการตรวจทางห้องปฏิบัติการพบผู้ป่วยทารกทั้ง 6 ราย ได้รับการตรวจเลือดยืนยัน chikungunya IgM ให้ผล บวก และ chikungunya PCR ให้ผลบวก 3 ราย ภาวะแทรกซ้อนพบ clinical encephalitis 2 ราย ไม่พบรายงานการเสียชีวิต **สรุป:** โรคชิคุงุนยาในทารกแรกเกิด ทารกสามารถรับการถ่ายทอดเชื้อไวรัสจากมารดาที่ติดเชื้อและแสดงอาการคล้ายคลึงกับ neonatal sepsis ทำให้ไม่สามารถแยกออกจากกันได้อย่างชัดเจน ดังนั้นหากเกิดในพื้นที่ที่มีการแพร่ระบาดของโรคชิคุงุนยาในขณะนั้น จำเป็นต้องคิดถึงโรคชิคุงุนยาในทารกแรกเกิดที่มาด้วยอาการแสดงคล้ายการติดเชื้อในกระแสเลือดหรือระบบประสาทส่วนกลาง ไว้ด้วยเสมอเนื่องจากแนวทางการรักษาแตกต่างกันและทารกอาจมีภาวะแทรกซ้อนจากการติดเชื้อไวรัสชิคุงุนยาตามมา

คำสำคัญ: ชิคุงุนยา ทารกแรกเกิด การติดต่อแพร่กระจายจากแม่สู่ลูก อาการคล้ายการติดเชื้อในกระแสโลหิต

Background

Outbreaks of chikungunya fever have been reported in Asia, Africa, Europe, and in countries and territories in the Indian Ocean and the Pacific Ocean. Chikungunya fever is caused by infection of RNA viruses belonging to the Alphavirus genus in the Togaviridae family. The vectors responsible for the transmission of chikungunya virus infection are infected female *Aedes aegypti* and *Aedes albopictus* mosquitoes. In Thailand, the disease was first reported in 1958, during a concurrent dengue fever outbreak and outbreaks of chikungunya were later reported in 2008 in Southern Thailand.¹ The

re-emergence of chikungunya outbreaks was subsequently reported from June to October 2019 in Mae Sot District, Tak Province,² in Thailand's Western region, on the Myanmar border. The incidence of chikungunya fever in children is relatively low when compared to adults, especially among newborns. Until recently, there had been no reports of mother-to-child chikungunya virus infection in Thailand. Typically, a newborn develops signs and symptoms within a week of life after contracting the virus from his/her mother during pregnancy. The mother usually demonstrates signs and symptoms of chikungunya fever prior to delivery. This study was therefore intended to present results of the newborns who contracted chikungunya virus from their mother in Mae Sot District, Tak Province. Chikungunya virus infection was detected and confirmed by performing chikungunya immunoglobulin M (IgM) antibody and, or polymerase chain reaction (PCR) from blood samples.

Materials and Methods

This was a descriptive study using data collected from June to October 2019 from neonatal patients suspected of having contracted chikungunya virus from their mother. These newborns were hospitalized either in a pediatric intensive care unit (ICU) or nursery ward at Mae Sot General Hospital, Mae Sot District, Tak Province. Mothers presented with signs and symptoms of fever, joint pain, and rash within one week prior to delivery, accompanied by confirmatory test results indicating chikungunya positive IgM antibody and, or positive PCR for both the newborns and mothers. The data collected included demographic information, sex, nationality, gestational age, mother's age, clinical presentations, routine laboratory results, chikungunya-specific laboratory findings. Data were analysed using descriptive statistics, and summarized using frequency, percent, mean, median, and range.

Results

Demographic data on six newborns who contracted chikungunya virus from their mothers, who gave birth at Mae Sot General Hospital, Mae Sot District, Tak Province, are shown in table 1.

Table 1 Demographic information of newborns affected by mother-to-child chikungunya virus infection

Demographic data	Number(N=6) (percent)
Sex	
Male	2 (33.3%)
Female	4 (66.7%)
Nationality	
Thai	3 (50.0%)
Burmese	3 (50.0%)
Mode of delivery	
Vaginal delivery (normal)	4 (66.7%)
C-section	2 (33.3%)
Gestational age (week)	
Term (37-41 weeks)	4 (66.7%)
Preterm (32-36 ⁺⁶ weeks)	2 (33.3%)
Birth weight (gram), median	3,225
> 4,000	1 (16.7%)
3,000-4,000	2 (33.3%)
2,000-2,999	3 (50.0%)
Mother's age (year),median	24
15-25	4 (66.7%)
26-35	1 (16.7%)
36-45	1 (16.7%)

Four of the six newborns (66.7%) were female. Fifty percent were Thai. Majority had normal delivery (n=4, 66.7%). The average gestational age (GA) was 37.8 weeks; two (33.3%) neonates were born prematurely (32- 36⁺⁶weeks). Median weight at birth was 3,225 g and half had a birth weight within the range of 2,000-2,999 g. The mothers' median age was 24 years; most were 25 years or younger.

Signs and symptoms

Of the 6 newborns evaluated, all developed fever with concurrent maculopapular rash, around day 4-5 of life. Signs and symptoms observed in five newborns

(83.3%) included edema, irritability, respiratory distress, and hyperpigmentation. Edema was usually present on the torso and limbs. Hyperpigmentation normally appear following the resolution of maculopapular rash at 9–10 days of life and it was highly noticeable on the face, nose, and around the mouth (acrofacial hyperpigmentation) and the torso (Figures 1 and 2). Other signs and symptoms included poor feeding (observed in three newborns (50%), seizure and clinical encephalitis (33.3%), and hemodynamic instability (16.7%) as shown in table 2.

Table 2 Signs and symptoms of newborns suspected of contracting chikungunya virus during pregnancy (N=6)

Signs/Symptoms	Number (percent)
Fever	6 (100%)
Maculopapular rash	6 (100%)
Diffuse/limbs edema	5 (83.3%)
Irritability	5 (83.3%)
Hyperpigmentation	5 (83.3%)
Respiratory distress	5 (83.3%)
Poor feeding	5 (50.0%)
Seizure	2 (33.3%)
Hemodynamic instability	1 (16.7%)



Figure 1, 2 Acrofacial hyperpigmentation on the face, around the mouth and nose (brownie-nose hyperpigmentation) and torso

Table 3 Routine laboratory findings

Patient No.	WBC [$10^3/\mu\text{l}$] Median [min-max]	PMN (%) Median [min-max]	Lym (%) Median [min-max]	Platelet [$10^3/\mu\text{l}$] Median [min-max]	Hb (g/dL) Median [min-max]	Hct (%) Median [min-max]	Other AST,ALT (U/L) Albumin (g/dL)
1	15.9 [9.9-17.6]	47 [17.1-93.9]	40.9 [3.4-71.8]	78 [18-322]	17.3 [14.8-23.2]	52.3 [45.8-69.8]	AST=157, ALT=23, Albumin=2.5
2	12.6 [7.2-19.7]	53.6 [29-85]	32.7 [7.2-55]	81.5 [58-403]	16.1 [13.4-16.3]	47.4 [39.9-49]	AST=113, ALT=35, Albumin=3
3	9.0 [7.1-12.5]	49.8 [28-92.9]	41.6 [3.1-61.2]	130 [52-483]	13.6 [11.2-15]	40 [33-43.9]	AST=213, ALT=34, Albumin=2.2
4	19.4 [3.9-25.9]	66.1 [32.7-92.4]	17.1 [4.2-70]	57 [23-267]	13.35 [9.5-20.5]	38.9 [28.2-60.2]	AST=354, ALT=41, Albumin=2.7
5	11.8 [4.2-18.7]	57 [18-94.9]	21 [2.7-55]	64 [12-412]	12.5 [9.1-17.1]	37.7 [25.6-51.2]	AST=216, ALT=51, Albumin=2.1
6	6.4 [5.7-15.3]	65 [42.6-75.8]	25.7 [13.2-48.9]	113 [89-190]	17.4 [16.5-18.2]	51 [49.8-54.4]	-

Based on a complete blood count (CBC) profile, it was found that the newborns enrolled in this study had shown white blood cell (WBC) count as viral infection the range of 6,400-19,300/ μl , neutrophil 47-66.1%, lymphocyte 21-41.6 %. Three in six newborns (50%) were anemia, Hemoglobin (Hb) was less than 14 g/dL. All patients had thrombocytopenia with a platelet count between 57-130 $\times 10^3/\mu\text{l}$.

Liver function test (LFT) profile from five patients indicated that all patients had abnormal laboratory results, i.e. aspartate aminotransferase (AST) levels were higher than 2 times of upper normal value. All newborns presented with edema had hypoalbuminemia in the region of 2.1-3 g/dL, while alanine aminotransferase (ALT) values for all patients were within normal limits.

Serum chikungunya antibody tests were performed on clinical specimens collected from six neonatal patients and the results came back positive for chikungunya IgM for all patients. As for chikungunya virus PCR, due to some limitations, samples from only three patients were

submitted for laboratory testing and the results were all positive for chikungunya PCR. Five in six (83%) mothers of all newborns had blood sample collected, chikungunya IgM antibody confirmatory tests were performed, and the results came back positive for all.

In addition, in parallel with chikungunya virus identification, laboratory diagnostic tests to detect dengue virus infection, including Dengue NS1Ag and Dengue IgM antibody, were conducted in parallel with chikungunya virus identification. No concurrent dengue virus infection had been identified in all patients.

Based on cerebrospinal fluid (CSF) tests five in six patients, one patient had pleocytosis due to trauma. Other CSF parameters for this case included WBC 48 cell/ mm^3 ; neutrophil 80%; lymphocyte 20%; protein 200 mg/dL; and RBC 26,500cell/ mm^3 .³ Three out of four had RBC between 2-10 cell/ mm^3 .³ Seizure was observed in two patient, one patient CSF profile presented WBC 28 cell/ mm^3 and neutrophil 100% and the other one had not found WBC. Four in five patients CSF protein and glucose

levels were found to be in a normal range. No bacterial pathogens were identified from CSF samples of all five patients.

All six newborns received supportive treatment. Transcranial ultrasound was performed on two neonates who experienced seizure and developed clinical encephalitis and no abnormal findings were obtained. Due to some limitations, it was not possible to send CSF sample for chikungunya PCR tests. The newborn who experienced hemodynamic instability was treated with intravenous fluid administration, vasoactive drugs, and intubation. The conditions of all six newborns were constantly improving. An average hospital stay was 21.7 days. Following discharge, follow-up visits were regularly performed to monitor the patients. The significantly complications had not been reported

Discussion

Chikungunya virus can be transmitted from mother to child if the mother is infected with the virus and shows clinical signs during one week before delivery. The incidence of mother-to-child chikungunya virus transmission was first reported in the French Territory of Réunion Island located in the Indian Ocean during 2015-2016, during which the peak of the outbreaks of chikungunya fever took place. During the outbreaks, it was found that 8.3 percent of chikungunya-infected pregnant women had transmitted the virus to their newborns.³ Mother-to-child chikungunya virus transmission can occur at any stage of pregnancy. In particular, if the infection occurs during the first trimester of pregnancy, there will be an increased risk of miscarriage.⁴ If the mother has clinical signs or viremia during the intrapartum period this will maximize vertical transmission of the virus, potentially resulting in up to 50 percent of symptomatic illness in newborns and increased risk of serious medical conditions. In addition, recent studies indicate that cesarean section delivery cannot help prevent mother-to-child vertical transmission.⁵

The most common signs and symptoms observed in the newborns affected by chikungunya fever during this study included fever, rash, edema, respiratory distress, and

poor feeding. These findings are consistent with those in the previous study by Ritz-N et al. Six patients indicating that the average onset of symptoms among infected newborns was around 4–5 days after birth and within 7 days of life. It should be noted that the symptoms did not appear immediately after delivery. The most common clinical signs included fever, rash (petechial, bullous and maculopapular rash and desquamative lesions), swelling (diffuse limb edema), lethargy, poor feeding, tenderness, unexplained apnea, and sepsis-like syndrome.⁶

In this study, one of the important clinical signs was skin rash, most notably as maculopapular rash, which was observed during 1-2 days after fever onset. This was followed by the presence of hyperpigmentation on days 4–5, which was clearly visible on the face, nose, and around the mouth (i.e. acrofacial hyperpigmentation) and then further spread to torso and upper and lower limbs. These dermatological findings were the consequence of inflammation following chikungunya virus infection, which induced an accumulation of melanin within the epidermis.⁷ During the follow-up visits to monitor all six patients, hyperpigmentation was found to persist for up to 1-2 months after the onset date. The rash faded away and finally settled completely. Serious complications observed during this study included seizure, encephalitis, and hemodynamic instability. Transcranial ultrasound was performed on two patients suffering from seizure and no intraventricular hemorrhage was detected. However, it could not be definitively concluded that there were no brain abnormalities as a brain MRI was not performed.

In general, neurological involvements typically found in the neonates who had contracted chikungunya virus from their mothers included seizure, meningoencephalitis, and encephalopathy. Brain MRI results indicated abnormalities in white matter in the frontal, parietal, peri-ventricular, and subcortical regions, subsequently resulting in hypertonia/hypotonia. And if a repeat brain MRI is obtained, other abnormal findings may also include cystic encephalomalacia, ventricular dilatation, and diffuse brain atrophy.⁸

Recent studies in Colombia has indicated that neurological complications as a result of chikungunya virus

infection have had a long-term impact on the newborns, potentially leading to cerebral palsy. Given the potential long-term effects, there is a need for continued monitoring of the patients for at least 2 years.⁹

Other severe complications observed in the newborns affected by mother-to-child chikungunya transmission included multiple organ involvement, e.g. renal failure, necrotizing enterocolitis, meningoencephalitis, myocarditis, pericarditis, sepsis, and disseminated intravascular coagulation (DIC). Some patients developed fatal complications such as necrotizing enterocolitis and gastrointestinal bleeding.¹⁰

CBC profile obtained from this study indicated all three types of hematological abnormalities including anemia (Hb<14 g/dL)¹¹, leukopenia, and thrombocytopenia. These findings were consistent with a recent study in Colombia, which described that Hb and Hct levels had markedly dropped in the chikungunya affected newborns. Thrombocytopenia ($<100 \times 10^3/\mu\text{l}$) in newborns was apparently more severe when compared with older children or adults¹². During this study, all patients had thrombocytopenia and three had an extremely low platelet count ($< 50 \times 10^3/\mu\text{l}$). It took nearly 1-2 weeks for the platelet count to return to a normal level. Platelet transfusion was given to patients suffering from thrombocytopenia. After constantly monitoring for potential gastrointestinal bleeding, no abnormal bleeding has occurred. As in older children and adults, management of neonatal patients infected by chikungunya virus was mainly supportive. An extended follow-up period may also be necessary, cause neurological implications like cerebral palsy and neurocognitive impairment can have a long-term detrimental effect on the newborns.¹²

This study was limited by a small sample size and some logistical issues, making it impossible to transport

samples from all patients for confirmatory laboratory tests. Nevertheless, clinical signs of the newborns and their mothers, i.e. fever, rash, edema, and joint pain, which typically occur within 1 week before and after delivery may be a key to diagnose chikungunya fever in the future, particularly in the area where the outbreaks of chikungunya fever in pregnant women are being reported.

It is apparent that neonates affected by mother-to-child transmission of chikungunya virus have demonstrated clinical signs and symptoms as well as CBC profile similar to those of neonatal sepsis and most neonatal patients were administered antibiotics. Therefore chikungunya fever should always be suspected for any newborns with clinical sepsis in the areas where the outbreaks are reported. The newborns affected by mother-to-child chikungunya virus transmission should be monitored closely for severe complications.

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