



Atypical Chikungunya during pregnancy: Report of the Venezuela final experience

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ABSTRACT

Introduction

Chikungunya virus (CHIKV) is an emerging arbovirus in Latin America and the Caribbean. The virus was detected in the Caribbean territory, at the end of 2013 for the first time. It is known that 1 to 2 % of patients will show atypical symptoms.

Methods

Three cases of pregnant women with atypical Chikungunya virus are described taking into account epidemiological variables, clinical features, pregnancy progress and laboratory testing parameters.

Results

Three pregnant women with atypical CHIKV confirmed by RT-PCR were included. All of them were included at the ICU because of a life-threatening disease, 2 of the pregnancies were resolved by caesarean, one at term with a newborn with typical CHIKV and the other one at the 25 week of pregnancy, this result in a stillborn and a neonatal death.

Conclusion

Chikungunya fever during pregnancy can show atypical and severe course, with adverse evolution of pregnancy and vertical transmission of the infection. We recommend to maximize the medical care in pregnant women with suspicion of CHIKV infection.

Keywords: Chikungunya, Pregnancy, Atypical Chikungunya, Chikungunya Outbreak

INTRODUCTION

Chikungunya virus (CHIKV) is an emerging arbovirus in Latin America and the Caribbean.¹ This virus cause Chikungunya fever characterize by sudden high fever and joint symptoms that can be severe. In general, 1 to 2% of cases can show atypical signs with a range of severity.²

The most vulnerable groups are the elderly, patients with comorbidities, newborns and pregnant women.³

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It is transmitted by the bite of the *Aedes* mosquito. Other transmission ways are perinatal, occupational and potentially through transfusions.⁴⁻⁶

There is still lack of evidence regarding vertical transmission of CHIKV in Latin America. However, up to date 180 cases within 5 countries have been reported.⁷⁻¹⁰

GOAL

To analyze clinical and laboratory testing features and the evolution of 3 pregnant women with confirmed severe atypical Chikungunya.

METHODS

Three particular cases of pregnant women with atypical Chikungunya are described (table 1) taking into account epidemiological variables, clinical features, pregnancy progress and laboratory testing parameters. All of them were received in the setting of Chikungunya Fever epidemic in Venezuela during 2014.

RT-PCR was carried out for the diagnosis in the National Institute of Hygiene "Rafael Rangel". Serology for Dengue and HIV, and immunologic tests were carried out in order to discard other diseases.

RESULTS

Case 1

A 24 years old pregnant woman (first pregnancy), 37 pregnancy weeks plus 6 days. 4 days previous to admission noticed malaise, fever 39.00°C, bilateral arthralgia in ankles, edema and pain on both plantar areas and abdominal rash. 24 hours after admission suddenly showed tachypnea, hypoxia (SO₂: 67%), tachycardia (130 ppm), hypotension, and retrosternal pain. The EKG reported sinus tachycardia. The Cardiac enzymes were normal. The patient was transferred to the Intensive Care Unit (ICU) and Caesarea was carried out. Immediately after the procedure the symptoms disappear. The newborn presented symptoms of typical chikungunya at the second day of birth

Case 2

A 25 years old pregnant woman (second pregnancy), 25 weeks of multiple pregnancy. The patient is admitted with premature delivery threat, urinary

infection, fever and generalized arthralgia. The next day the patient showed frequent uterine contractions resistant to Fenoterol. The patient is treated with Magnesium Sulfate and suddenly showed tachypnea, tachycardia, neurologic failure (stupor and agitation), retrosternal pain and hypoxia.

An emergency Caesarea is carried out obtaining a stillborn and a newborn with neonatal death in 48 hours. The patient is transferred to other health center to be admitted in ICU where needed mechanical ventilation during 72 hours. The patient is discharge afterwards in good conditions.

Case 3

A 19 years old pregnant woman (second pregnancy), with 20 pregnancy weeks. Is admitted because of fever. The next day showed rash and pruritus in abdomen and lower limbs, generalized arthralgia and arthritis in interphalangeal joints of both hands, wrists (Figure 1) and ankles. Also bilateral edema (Figure 2) making impossible to walk. Laboratory testing showed anemia, leukocytosis and neutrophilia.

14 days after admission showed dyspnea, tachycardia and bilateral pleural effusion. Is admitted in ICU during 10 days where differential diagnosis sepsis and immune-rheumatologic disease were ruled out. While waiting for culture results empiric antimicrobial therapy with Vancomycin and Meropenem was started.

The patient was discharged after 33 days of hospitalization in good conditions, with 24 + 6 days of pregnancy and a healthy fetus.

Table 1 shows the clinical and laboratory characteristics and the evolution of pregnancy in the three cases.

CHIKV diagnosis was confirmed in all patients through genomic identification of the virus using RT-PCR. Serology for dengue, VDRL, CMV and HIV were negative in all cases. Also all the bacterial cultures were negatives.



Fig 1 Generalized Arthralgia and Arthritis in Interphalangeal Joints of Both Hands and Wrists



Fig 2 Bilateral Edema

Table 1 Characteristics of the Patients with Chikungunya

Cases	Age	Pregnancy weeks	Symptoms	Cardiac and respiratory maternal symptoms	Pregnancy progress	Vertical transmission / Newborn progress	Test CHIKV	Other Tests
Nº 1	24	37	Arthralgia in ankles, edema and bilateral plantar pain, abdominal rash.	Tachycardia, dyspnea, hypotension, thorax pain, and hypoxia. Admitted in ICU 48 hours.	At term (Caesarea)	Newborn with typical CHIKV (RT-PCR for VCHIK not available)	RT-PCR positive	Leucopenia, lymphocytosis. EKG: sinus tachycardia. Normal cardiac enzymes.
Nº 2	25	25	Fever, generalized mio-arthralgias.	Dyspnea, tachycardia, neurological failure, retrosternal pain and hypoxia. Admission in IUC during 3 days.	Preterm (Caesarea)	Newborns (twin pregnancy) preterm, a stillborn and a newborn who died in 48 hours. (RT-PCR for CHIKV not available).	RT-PCR Positive	Leucopenia. EKG: sinus tachycardia. Normal cardiac enzymes.
Nº 3	19	20	Fever, maculopapular rash, arthritis in both hands, wrists, toes of both feet and ankles.	Tachycardia, dyspnea and serosytis. Admission in ICU during 10 days.	Without obstetric complications.	Discharge at day 33th, ulterior progression of pregnancy unknown.	RT-PCR Positive	Leukocytosis with neutrophilia. C protein reactive, VSG, hepatic enzymes and DHL increased. Thrombocytopenia and immunologic tests: negative. EKG: sinus tachycardia.

DISCUSSION

Chikungunya fever is an emerging arbovirosis in the Americas which is caused by the homonymous virus. The word Chikungunya comes from the Makonde language which means "to get dry or to get buckled", due to the bended habitus of the patients because of the pain.¹² It was identified for the first time in Tanzania during 1952 – 1953.¹³

The virus was detected in the Caribbean territory, at the end of 2013 for the first time, specifically in the San Martin Island on its French part¹⁴ and it was rapidly spreaded to other Caribbean islands and the Americas, happening to meet its presence with the areas of the transmitter vectors, the *Aedes spp.* Mosquitoes.^{14, 15}

According to the Pan American Health Organization (PAHO), during 2014, 1.071.696 cases were detected in the Americas, while 169 died.¹⁶ The first autochthonous case in Venezuela, was reported in June 2014.¹⁷ Until the 51th epidemic week in 2014, Venezuela reported 34.642 suspected cases while 2303 confirmed to the PAHO (PAHO). This data differs from the one estimated by Public Health Venezuelan specialists (*Defendamos la epidemiología* network and Venezuelan Society of Public Health); which estimated almost 3 million cases of CHIKV in our country.¹⁸

Studies on Chikungunya Fever during pregnancy were carried out during the first epidemic in the

Reunion Island in 2006, and showed similar clinical features between this group and non pregnant population.¹⁹

Out of 658 pregnant women infected with CHIKV, the most frequent signs and symptoms were: Fever (62%), arthralgia (93%), cephalgia (54%), edema (54%), diarrhea (12%), aphthous ulcers (9.6%), epistaxis or gingivorrhagia (9.0%) and rash (76%). In total, 137 (21%) were admitted with a mean of 2 days of inpatient permanence (rank 1-75 days), atypical manifestations were not described.¹⁹

Atypical symptoms of Chikungunya fever are shown in a low proportion of patients and they have a wide spectrum. Ulterior series have described: encephalitis, seizures, myocarditis, pericarditis, heart failures, renal failure, respiratory failure, ocular affection (episcleritis, granulomatose and non granulomatose uveitis, etc.), hyperpigmentation and epidermolysis bullosa, among others.^{2, 20-30}

Reports on atypical Chikungunya in pregnant women is limited. This study represents the first case series of atypical and severe presentation of Chikungunya during pregnancy in Venezuela.

The cases 1 and 2 showed similar clinical features: tachycardia, dyspnea, retrosternal pain. The case 3 also showed tachycardia and dyspnea apart from other already mentioned symptoms. The newborn of the case 1 showed clinical features of typical Chikungunya fever, with generalized maculopapular rash and fever.

Vertical transmission of CHIKV was demonstrated for the first time in the epidemic in the Reunion Island in 2005-2006, where the rate was low. However, vertical transmission rates up to 48.7% can be seen when the acute infection occurred during the peripartum, particularly when the mother acquired CHIKV in the last week before the delivery.^{19, 24}

In Colombia, at the Sucre department (state), the first report of 8 babies with a confirmed perinatal-acquired CHIKV (either documented with RT-PCR and/or serology) was published in August 2015.⁸

A few months later, at the Santander department (state), one additional case reported residual psychomotor sequelae after 12-month follow up.²⁵ In July 2016, two other cases were documented (with RT-PCR confirmation both in serum and urine) in Salvador, Brazil.^{9, 10}

In these case series, as well as in others,^{8-10, 25} the attention was focus to life-threatening complications requiring support of vital functions in the neonatal intensive care unit, such as meconium-stained aspiration pneumonia, sepsis, necrotizing enterocolitis, severe respiratory distress, myocardiopathy, encephalopathy or bullous dermatosis.

In September 2016, the first initiative of data sharing about the topic was published as a multicenter study conducted in four large regional maternity units from three different countries in Latin America.²⁶ The report included 169 newborns observed in El Salvador, Colombia and Dominican Republic. The clinical presentations presumably due to the Asian lineage of CHIKV were consistent with those previously reported from Reunion Island with a lower incidence of neurological disease but a higher case fatality rate than expected with the Indian-Ocean lineage.⁷

Recently in Puerto Rico ten additional cases were reported,²⁷ which summarizes the Western Hemisphere experience with at least 180 published cases gathered from 5 countries.

Chikungunya fever, is different to Zika virus because it has not been associated with congenital malformations. However, there are some reports of cognitive illnesses in newborns with atypical presentation of the disease.²⁸

The case 2 showed premature delivery with stillborn and neonatal death, probably associated with severity of the disease (hypoxia, tachycardia, dyspnea). Chikungunya fever can cause abortion and premature delivery,²⁹ on the other hand the prematurity is an important cause of neonatal death. The case 3 showed persistence of the symptoms (arthralgia, fever and rash), probably mediated by the

increase of interleukins IL-1 β , IL-6 and decrease of RANTES, which have been related to severe presentation.³⁰ This patient showed clinical features and laboratory parameters that have been described in atypical and severe CHIKV cases²⁰ like dyspnoea, tachycardia, serositis, leucocytosis, anaemia, thrombocytopenia, and high hepatic enzymes. Due to high levels of LDH plus the findings mentioned, HELLP syndrome was suggested initially. This condition can be diagnosed with biochemical markers, although some experts require the presence of severe pre-eclampsia plus the biochemical markers.³¹ This patient didn't show hypertension and the progress of the pregnancy during the hospitalization was normal and pregnancy was not interrupted.

The differential diagnosis of atypical CHIKV in pregnancy include severe Dengue, severe Zika, Mayaro Fever, cytomegalovirus acute infection, acute Chagas, Malaria, viral Hepatitis, sepsis, other causes of cardiac diseases, HELLP syndrome and eclampsia, among others.³¹⁻³⁶

In this study the diagnosis of all cases was confirmed with RT-PCR, which must be carried out the first 5-6 days of the disease. After the viremia phase other serologic tests more accessible like ELISA can be used. However, the essays for the detection of antibodies like ELISA test are not recommended during the acute phase.³⁷

The medical care of pregnant women with atypical CHIKV is complex, and require multidisciplinary attention, including infectious diseases specialists, internists, obstetricians and intensivists.

CONCLUSION

Chikungunya fever during pregnancy can show atypical and severe course, with adverse evolution of pregnancy and vertical transmission of the infection. We recommend to maximize the medical care in pregnant women with suspicion of CHIKV infection. This is the first report of pregnant women with atypical Chikungunya in Venezuela.

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