INTRODUCTION

Since its introduction in 2015, Zika virus (ZIKV) has produced multiple outbreaks in South America. Contracted through the bite of an infected mosquito or through sexual contact, ZIKV infection may impair fetal development when transmitted during pregnancy. Congenital Zika syndrome (CZS) is a constellation of neurodevelopmental abnormalities; however, this spectrum is not limited to the brain as it also encompasses cardiovascular compromise and bone-related disorders. In 2019, the largest ZIKV outbreak in Peru occurred in Jaén, a high jungle city in the Cajamarca region. We report the case of an infant born with CZS with broad clinical manifestations.

CASE REPORT

A 27-year-old woman presented at 10 weeks of pregnancy with a pruriginous generalized rash associated with malaise and subjective fever. She did not experience non-purulent excretions and assessment of cranial nerves were normal. Fundoscopy was unremarkable.

Obstetric ultrasounds were unremarkable until the 25th week of pregnancy when findings suggested intrauterine growth restriction (IUGR). A thorough assessment at week 27 confirmed severe IUGR with an estimated fetal weight of 1,003 g (< first percentile), microcephaly (< 3 SDs), and lissencephaly. In addition, periventricular, basal ganglia and intraparenchymal calcifications were reported. Cardiovascular findings included right ventriculomegaly (11 mm) and mitral valve calcification. She had received all the recommended immunizations for pregnancy according to national guidelines. Serum IgG for rubella, Toxoplasma, and cytomegalovirus (CMV) were positive.

She delivered a baby boy at 36 weeks and 5 days gestational age. He weighed 1,900 g (< third percentile), was 45 cm long (between 10th and 50th percentile), and had a head circumference of 28 cm (< third percentile). He presented prominent microcephaly, retrognathia, and valgus deviation of lower extremities with a left clubfoot (Figures 1 and 2). Serum IgM for CMV and Toxoplasma were indeterminate, and IgM for herpes simplex virus 1 and 2 were negative. ZIKV testing was not performed on clinical samples collected from the neonate; likewise, genetic testing such as microarray testing or karyotyping was not performed because of testing limitations in the region.

At 2 months of age, the infant was thoroughly evaluated. He was irritable and appeared malnourished with weak suction. He had a punctiform anterior fontanelle and presented with obvious anatomic anomalies. A grade I/VI systolic murmur was audible over the precordium. The echocardiogram revealed mild hypertrophic cardiomyopathy with diastolic dysfunction and indirect signs of pulmonary hypertension. Lower limb radiography reported longitudinal axis deviation and bilateral internal rotation, and hip ultrasound showed incipient signs of Graf type II dysplasia. The electroencephalogram was abnormal, showing asymmetric, low-frequency activity predominantly on the left hemisphere without paroxysms. Evoked auditory and visual potentials were reported as normal.

A grade I/VI systolic murmur was audible over the precordium. The echocardiogram revealed mild hypertrophic cardiomyopathy with diastolic dysfunction and indirect signs of pulmonary hypertension. Lower limb radiography reported longitudinal axis deviation and bilateral internal rotation, and hip ultrasound showed incipient signs of Graf type II hip dysplasia. Physical therapy sessions were scheduled to improve tone and global developmental delay. In addition, thorough counseling on breastfeeding with formula supplementation was given.

DISCUSSION

Congenital Zika syndrome exhibits various clinical features that are a direct consequence of severe intracranial volume loss and neurological damage. The most notable finding of CZS is microcephaly, which has been strongly associated with infection at early gestational weeks. Defined as head
circumference more than two SDs (or more than three SDs for severe microcephaly) below the mean or less than the third percentile for age and gender, microcephaly can be diagnosed pre- or postnatally. Although the rate of microcephaly in Cajamarca (the region where our patient is from) was higher than that reported in other countries before the introduction of ZIKV in South America, it is possible that this difference is explained by distinct measurement techniques or the use of standard curves in a population with smaller head circumferences. Nonetheless, we defined our case as CZS because of the clinical findings of the infant and the positive ZIKV RT-PCR from the mother during pregnancy.

Although microcephaly in obstetric ultrasounds allows for early detection of ZIKV-related cerebral manifestations, this method should not be considered for screening of CZS as other brain findings can be seen in imaging; these may include an underlying neuronal migration disorder due to impaired development of neuroprogenitor cells, which leads to ventriculomegaly and lissencephaly. Subsequent inflammation caused by the virus, manifested as intracranial calcifications predominantly at the junction between the cortex and subcortical white matter, basal ganglia, and thalamus can also be seen on ultrasound images. Depending on the extent of neural proliferation compromise, CZS has been found to cause sensory disabilities such as visual and hearing deficits. Furthermore, abnormal brain activity without epileptiform discharges has been described in 48% of children with CZS, although seizures have been described. Severe brain abnormalities impair development, and early termination of pregnancy is an option in some countries; however, the legislation in Peru does not allow for disruption of pregnancy unless the mother’s life is at risk.

In addition, cardiovascular compromise has a potential effect of ZIKV infection. Transient myocarditis, heart failure, and changes in repolarization leading to rhythm disorders, such as atrial fibrillation, non-sustained atrial tachycardia, and ventricular arrhythmia, have been reported in adult patients, whereas structural heart defects are a prevalent feature of in utero ZIKV exposure. Echocardiographic evaluations show mild ventricular and atrial septal defects, and, as with microcephaly, the frequency of major defects was higher in infants whose mothers had ZIKV exposure early in pregnancy or who had neurological anomalies in imaging. Our case did not present congenital structural defects or rhythm disorders; nonetheless, pulmonary hypertension and hypertrophic cardiomyopathy were reported. Some authors suggest timely screening among CZS cases due to potential undiagnosed cardiovascular complications. Currently, our case does not require any medication, but further follow-up has been scheduled.

Another cell lineage to which ZIKV has demonstrated tropism is osteoblast cells by disturbing their differentiation, maturation, and function. The presence of ZIKV on synovial fluid correlates with the development of arthralgias in primary infection, but the imbalance in bone homeostasis is due to impaired osteoblast function, which can induce bone-related disorders while the fetus is developing. Arthrogryposis, one of the most limiting extracranial conditions, involves multiple

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**Figure 1.** Prominent microcephaly and retrognathia. This figure appears in color at www.ajtmh.org.

**Figure 2.** Valgus deviation of lower extremities and left talipes equinovarus. This figure appears in color at www.ajtmh.org.

**Figure 3.** Computed tomography of the head. (A) Axial view, calcifications in the left thalamus. (B) Axial view, right occipital and bilateral temporal calcifications.
joint contractures, and its association with CZS has been described with flexed wrists as the most common finding. Other manifestations include talipes equinovarus (clubfoot), valgus deviation, and bilateral rotation of the lower limbs, and hip dislocation. Physical therapy is recommended to improve postural control and mobility, and has been suggested to improve this patient’s clubfoot and angulation of the extremities.

In the short time that ZIKV has emerged as a public health emergency in South America, CSZ has presented broad clinical manifestations in vertically transmitted infants. Microcephaly is perhaps the condition with the highest negative impact on the quality of life of affected infants and their families and should be seen as the tip of the iceberg of this syndrome. Interventions based on a multidisciplinary approach should be implemented to evaluate and monitor children with CZS and reduce the burden of the disease.

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REFERENCES


