Cerebral injuries associated with Zika virus in utero exposure in children without birth defects in French Guiana

Case report

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Abstract

Rationale: A major epidemic of Zika virus (ZIKV) infection occurred in French Guiana and West Indies. French national epidemiological surveillance estimated that 1650 pregnant women contracted the ZIKV during epidemic period from January 2016 to October 2016 in French Guiana.

Patient concerns: ZIKV infection during pregnancy is a cause of microcephaly and birth defects.

Diagnoses: In this report, we describe 2 children with proven in utero ZIKV exposure. Their mothers were both symptomatic and ZIKV infection occurred early in pregnancy. Ultrasonography monitoring in utero did not show any abnormality for both patient. They were born at full-term, healthy, without any birth defects and no sign of congenital ZIKV infection.

Interventions: ZIKV was neither found on placenta fragments nor children blood and urine at birth. Their neurodevelopment outcomes in early-life fitted the expectations. As recommended in national guidelines, we performed cerebral MRIs at 2 months old, showing severe brain abnormalities, especially of white matter areas. After a large screening, we did not find any differential diagnosis for their brain lesions.

Outcomes: We concluded it was due to their in utero ZIKV exposure.

Lessons: In this report, pathogenicity of ZIKV may involve mother’s immunological response or metabolic disorder during the infection.

Abbreviation: ZIKV = Zika virus.

Keywords: birth defects, neurological disorders, Zika virus

1. Introduction

Zika virus (ZIKV) infection during pregnancy is a cause of microcephaly and birth defects.<sup>[1–4]</sup> Congenital ZIKV infection is defined by specific clinical signs or by presence of Immunoglobulin M (IgM) antibodies in newborn blood or positive Zika polymerase chain reaction (PCR) on blood or urine sample at birth.<sup>[4]</sup> ZIKV in utero exposure only corresponds to proven maternal infection during pregnancy. A Brazilian team reported 13 cases of children...
born with congenital ZIKV infection and showed they had severe cerebral magnetic resonance imaging (MRI) abnormalities and developed secondary microcephaly. We describe 2 patients with proven in utero ZIKV exposure and without congenital infection, for whom MRIs showed severe abnormalities related to ZIKV exposure.

2. Case 1

This boy was born in December 2016. His mother was 32 years old, primigravida para2, and had no significant medical history. The first trimester serologies showed no sign of previous ZIKV infection, protective immunity against toxoplasmosis, rubella, and cytomegalovirus (CMV). HIV and hepatitis C virus were negative. She was immunized against the hepatitis B. The first fetal ultrasonography happened during first trimester and was normal.

In July, she developed rash, bilateral conjunctivitis, and low-grade fever. A ZIKV serology was performed using enzyme-linked immunosorbent assay techniques, showing presence of IgM and Immunoglobulin G (IgG) antibodies at high titer. Dengue and Chikungunya serology were performed showing no sign of previous or current infection. So we concluded it was a seroconversion at the end of first pregnancy trimester.

According to national recommendations, fetal ultrasonography was monitored monthly; hospital obstetricians performed a total of 5, none of which showed any fetal abnormality. She did not suffer from any other complication during pregnancy. There was no alcohol, tobacco, or other toxic consumption throughout gestation.

The mother delivered a healthy child at full-term. She had cesarean for stagnation of cervical dilatation after 7 hours of labor. The fetal heart rate was normal during labor. The newborn Apgar score was 10 at 1, 5, and 10 minutes, umbilical cord pH was 7.29 with lactate at 2.6 mmol/L. His measurements were 2970g (25th percentile), 48 cm length (15th percentile), and 34.5 cm for the head circumference (80th percentile). His clinical examination at birth and day 2 were normal. Blood tests routinely performed (hematology, biochemistry, liver tests, C-reactive protein), auditory evoked potentials at day 3 were normal. Bacterial samplings showed no sign of infection. A ZIKV PCR was practiced on placenta fragments and did not find the presence of Zika genome. We also performed ZIKV PCR at day 2 for the child in urine sample, which was negative. ZIKV serology performed at birth showed presence of IgG antibody, probably of maternal origin. Therefore, we concluded that there was no congenital ZIKV syndrome or infection and avoided further immediate exploration such as lumbar puncture.

First brain imaging was trans-fontanellar ultrasonography at day 22 and was normal. As recommended in national guidelines, brain MRI was performed at day 45. Key pictures are shown in Figure 1. The radiologist’s interpretation was as follows: “Diffuse MRI abnormalities with diffuse hyper intensity of white matter areas with predominance in both parietal areas, enlargement of Virchow-robin spaces, thin corpus callosum and cortical gray matter enlargement in temporal and parietal lobe. These lesions evoke an infectious footopathy.”

Entering the specific follow-up program, he was examined at 2 months of age; his measurements were 5130 g (40th percentile), 57 cm length (60th percentile), and head circumference 38 cm (40th percentile). His neurodevelopment outcomes fitted the expectations: primary reflexes had faded, he was able to hold his head when sitting, raise his head and shoulders from a prone position to a 45- to 90-degree angle from the table, smile, track objects and people, turn toward sounds, open his hand and grab a pen, vocalized, and babbled. His physical examination was strictly normal.

We made a large screening for viral or parasite agent known to confer infectious fetopathy with blood test at 2 months old. As we obtained the results, there was no sign of any other agent than ZIKV susceptible to have produced these cerebral injuries. CMV, epstein-barr virus (EBV), and Rubella serologies showed only presence of IgG antibodies that were of maternal origin. HSV1, HSV2, Parvovirus B19, and toxoplasmosis serologies were negative for both IgM and IgG antibodies. Treponema pallidum hemagglutinations assay (TPHA) and venereal disease research laboratory (VDRL) were negative as well. ZIKV PCR on blood and urine were negative. ZIKV serology performed only showed presence of IgG antibodies of maternal origin. Hematology, biochemistry, renal, and liver function were normal.

He was then examined at 4 months of age, his measurements were at 60th percentile for weight, length, and head circumference. His neurodevelopment outcomes fitted the expectations: he babbles using single consonants such as “baba,” smiles, laughs, and squeals responsively, was able to roll over from front to back, tries to pass toys from one hand to the other, got upset when separated from familiar person, sits with support. In the absence of any other infectious or toxic agent, we conclude that cerebral injuries found on this newborn are related to his in utero ZIKV exposure only.

3. Case 2

This boy was born in December 2016. His Mother was 36 years old, primigravida, and had no significant medical history. Ultrasonography pregnancy dating concluded that conception began on the March 28, 2016. ZIKV serology was performed a week before using enzyme-linked immunosorbent assay technique, for fever and rash by general practitioner. It showed IgM and IgG antibodies positive at high titer, confirming a recent ZIKV infection. Dengue and Chikungunya serology were performed showing no sign of previous or current infection. We concluded that ZIKV infection occurred in periconceptional period.

First trimester serologies were performed, showing protective immunity against toxoplasmosis, rubella, and CMV. HIV and hepatitis C virus were negative. She was immunized against the hepatitis B. Six fetal ultrasonography were performed, none of which showed abnormality. She did not suffer from any other complication in his pregnancy. There was no alcohol, tobacco, or other toxic consumption throughout gestation.

She delivered at full-term. The fetal heart rate was monitored and was normal during labor. Child Apgar score was 10 at 1, 5, and 10 minutes, umbilical cord pH was 7.18 with lactate at 3.6 mmol/L. His measurements were 3380 g (50th percentile), 48 cm tall (15th percentile), and the head circumference 36 cm (80th percentile). His physical exams performed at birth and day 2 old were normal. Blood tests, bacterial samplings, and auditory evoked potentials at day 3 were normal. A ZIKV PCR was practiced on placenta fragments, and did not find the presence of Zika genome. ZIKV PCR on urine was performed at day 2 for the child and was negative. ZIKV serology performed at birth showed presence of IgG antibodies probably of maternal origin. So, we concluded that there was no congenital ZIKV syndrome or infection and avoided further immediate exploration.
Figure 1. Patient number 1: Cerebral MRI showing diffuse white matter hyper intensity. T2 sequence. MRI=magnetic resonance imaging.
The first brain imaging was trans-fontanellar ultrasonography at day 36 and was normal. Cerebral MRI occurred at day 56 and showed comparable abnormalities as patient number 1. Key pictures are shown in Figure 2. Radiologist interpretation was as follows: diffuse hyper intensity of white matter areas with predominance in both parietal and occipital areas, enlargement of Virchow–Robin spaces. These lesions evoke an infectious fetopathy.

He was then examined at 2 months old; his measurements were 5070g (40th percentile), 56cm tall (50th percentile), and head circumference 38cm (40th percentile). His neurodevelopment outcomes also fitted the expectations (cf. patient number 1). His physical examination was strictly normal.

We screened the same infectious agents as for patient number 1. CMV, EBV, Rubella, parvovirus B19, HSV1 serologies showed only presence of IgG antibodies of maternal origin. HSV2 and toxoplasmosis serologies were negative for both IgM and IgG antibodies. TPHA and VDRL were negative as well. ZIKV PCR was negative on blood and urine. ZIKV serology only showed presence of IgG antibodies of maternal origin.

Figure 2. Patient number 2: Cerebral MRI showing diffuse white matter hyper intensity in occipital areas. T2 sequence. MRI=magnetic resonance imaging.
Hematology, biochemistry, renal, and liver function were normal. He was then examined at 4 months of age; his measurements were at 60th percentile for weight, length, and 70th percentile for head circumference. His neurodevelopment outcomes fitted the expectations. In the absence of any other infectious or toxic agent, we also concluded that cerebral injuries found on this newborn were related to the in utero ZIKV exposure only.

4. Discussion

In this article, we report 2 cases of children, both exposed in utero to ZIKV early in gestation, without any birth defect or congenital ZIKV infection that presented severe MRI abnormalities at 2 months of age. We did not perform fetal MRI because fetal ultrasonographies showed no sign of congenital infection for both children. We decided not to perform lumbar puncture or other invasive gesture for our patients, because they were absolutely asymptomatic and we could not propose any specific treatment.

ZIKV is known to have specific tropism and toxicity for the central nervous system, but its pathogenicity needs further exploring. There are several hypothesis: direct neuronal destruction by the virus; liver damage due to ZIKV, transitory hypervitaminosis A and resulting perturbations in retinoid metabolism during the critical period of embryogenesis; neuronal destruction due to an immunological response to the viral infection. For our cases, we did not find any clinical or biological sign of congenital infection; therefore, we believe the physiopathology of brain injuries cannot be explained by direct neuronal toxicity.

Our work is the first report on neurological abnormalities due to ZIKV in utero exposure only. Although the prognosis significance of the MRIs abnormalities remains unknown, our findings suggest the necessity of routine cerebral imaging on children exposed to ZIKV in utero in their first year of life. Our work surely supports the necessity of appropriate pediatric follow-up for those children.

In French Guiana, this specific follow-up program begins at birth containing 5 consultations at 2, 4, 9, 18, and 24 months old. A national multicentric epidemiological protocol on neurologic outcomes of exposed children started jointly on September 2016 called ZIKA-DFA-BB.

References

[1] Teixeira MG, Costa MDeC, Olivera WK, et al. The epidemic of Zika virus-related microcephaly in Brazil: detection, control, etiology, and future scenarios. Am J Public Health 2016;106:601–5.
[2] Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly—Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65:59–62.
[3] Pomar L, Malinger G, Benoist G, et al. Association between Zika virus and foetopathy: a prospective cohort study in French Guiana. Preliminary report. Ultrasound Obstet Gynecol 2017;49:729–36.
[4] Situation épidémiologique du virus Zika aux Antilles et en Guyane. Point au 23 février 2017. INVS, santé publique France 2017. Available at: http://invs.santepubliquefrance.fr/fr/Publications-et-outils/Points-épidémiologiques/Tous-les-numeros/Antilles/2017/Situation-épidémiologique-du-virus-Zika-aux-Antilles-et-en-Guyane-.Point-au-23-fevrier-2017. Accessed February 28, 2017.
[5] van der Linden V, Pessoa A, Dobyns W, et al. Description of 13 infants born during October 2015–January 2016 with congenital Zika virus infection without microcephaly at birth—Brazil. MMWR Morb Mortal Wkly Rep 2016;65:1343–8.
[6] Infection par le virus Zika. Prise en charge des nouveau-nés et nourrissons. Avis du 21 mars 2017. Haut conseil de la santé publique. Available at: http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=545. Accessed March 21, 2017.
[7] Mlakar J, Korva M, Tul N, et al. Zika Virus Associated with Microcephaly. N Engl J Med 2016;374:951–8.
[8] Mawson AR. Pathogenesis of Zika virus-associated embryopathy. Biores Open Access 2016;5:171–6.
[9] Valentine G, Marquez L, Pammi M. Zika virus-associated microcephaly and eye lesions in the newborn. J Pediatric Infect Dis Soc 2016;5:323–8.