A comprehensive review for the practitioner

Ashley Howard, DO
Pediatric Resident
Driscoll Children’s Hospital

Zika Virus and Congenital Zika Syndrome:

Can an infant with prenatal exposure to the Zika virus and does not exhibit microcephaly at birth still have congenital Zika-related birth defects?

Yes

No

Which of the following are possible congenital Zika-related birth defects?

- Microcephaly or brain abnormalities
- Neural tube defects/other early brain malformations
- Eye abnormalities without brain abnormality included in the first two categories
- Joint Contractures/Congenital sensorineural deafness
- All of the above
Objectives

- Define Zika virus, including its origins and mode of transmission
- Define the epidemiology of the Zika virus outbreak
- Understand and identify the clinical symptomatology to diagnosis Zika virus
- Apply and understand the principles of teratogenicity in regards to Zika virus
- Define and characterize Congenital Zika Syndrome
- Understand the current scientific mechanism of how Zika virus infection during pregnancy causes Congenital Zika Syndrome
- Define and explain the CDC guidelines on who should be tested for Zika Virus
- Define and explain the CDC standard of care guidelines for infants and children diagnosed with Zika Virus
Origin

- First discovered in 1947 in Uganda’s Zika Forest within the Rhesus/Macaque monkeys
  - Prior to 2007 only 14 human cases of Zika virus reported
  - 2007 first outbreak on Yap Island – 108 people
  - 2013 French Polynesia = 30,000 people
- Mosquito-borne flavivirus transmitted by Aedes aegypti and albopictus
- Other flaviviruses:
  - Dengue, Chikungunya, Yellow Fever, West Nile
Corpus Christi Mosquito Traps

World Map of Areas with Risk of Zika

2016 and 2017 Combined Data:
5,617 cases of Zika in the US with 231 cases of local transmission
69 Viremic Blood Donors
21 cases of Zika in the US with 2 cases in Texas and 0 cases of local transmission

1 Viremic Blood Donor

• Local transmission—First case confirmed 8/1/16 and to date with locally transmitted 220 cases

• Cautionary area lifted on June 2, 2017
Texas has 365 cases of travel associated infections and 11 cases of local transmission in Brownsville, the first confirmed on 11/28/16. The cautionary area was lifted on August 29, 2017.

**Viremia**

- Pre-symptomatic period of 3-12 days during which viremia occurs
- Viremia can produce up to 8.1 million copies/mL of serum
- Viremia typically lasts 1-2 weeks, but may last longer

*Published February 2017
Prospective Cohort Study*
Enrollment and Collection

- Ponce, Puerto Rico
- 150 participants tested positive for ZIKV on RT-PCR
  - Fever > 38.0°C
  - Rash
  - Conjunctivitis
  - Arthralgia
- 92% of participants were enrolled within 1 week after symptom onset
- Specimens were collected at 2, 4, and 6 months
- If ZIKV detected at 4 weeks, biweekly collection continued until all the specimens were negative

Persistence of ZIKV in Serum

CDC recommends that women wait 8 weeks after symptom onset or last exposure before attempting conception. (8 weeks = 56 days)

Persistence of ZIKV in Urine
CDC recommends men should abstain from sex for at least 6 months or use condoms to prevent sexual transmission.
Prospective Study

- 88 Women enrolled from Sept 2015-Feb 2016 in Rio de Janeiro, Brazil

  **Inclusion Criteria**
  - A woman at any week of gestation who presented to the acute febrile illness clinic at Oswaldo Cruz Foundation
  - Must have developed a rash within 5 days
  - No diagnosis of fetal malformations in current pregnancy
  - Negative VDRL, Rubella, and CMV
  - No maternal co-existing conditions
  - No maternal medication use

Protocol

- Blood and Urine samples were taken at enrollment
  - Tested for Zika with RT-PCR
  - Tested for IgG antibodies to Dengue
- Weekly telephone follow-ups
- Second clinical follow-up within 30 days

- Fetal Ultrasounds
  - Before 20 weeks
  - Between 20-30 weeks
  - After 30 weeks

Results of Testing

- 72 Women ZIKV + in blood, urine, or both (88%)
  - 26 + in blood only
  - 12 + in urine only
  - 34 + in both
- 16 Women ZIKV – (12%)
Figure A: Maculopapular rash on face

Figure F: Maculopapular rash on inner arm

Figure H: Blanching macular rash on gravid abdomen
Conjunctival Injection

- Figure B: Conjunctival and palpebral erythema
- Figure D: Conjunctival Injection with prominence of vasculature

Lymphadenopathy

- Figure C: Retro-auricular lymphadenopathy
Ultrasound

- All 16 ZIKV negative women had normal prenatal US
- 42/72 ZIKV + women underwent prenatal US
  - 2 miscarriages during the first trimester
  - 28 women declined due to:
    - Obstetrical facility too far
    - Fear of possible fetal abnormalities

Results

Outcome

- 12 of the 42 ZIKV + women who had fetal US had a detected abnormality (29%):
  - 2 fetal deaths at 36 and 38 weeks gestation
  - Infection had occurred at 25 weeks and 32 weeks
  - IUGR with microcephaly = 4 fetuses
  - IUGR without microcephaly = 1 fetus
  - Ventricular calcifications or other CNS lesions = 7 fetuses
  - Abnormal cerebral or umbilical artery flow = 4 fetuses
  - Oligohydramnios/Anhydramnios = 2 fetuses
Teratogens: An agent a mother is exposed to during pregnancy that has a harmful effect on her fetus.

Two Approaches to Identifying a Potential Teratogen

1. “Astute Clinician Approach”
   - Identification of a rare exposure and a rare defect
     - Ophthalmologist noted characteristic form of cataracts in infants whose mothers had Rubella during pregnancy
     - Recognition of characteristic pattern of malformations — Fetal Alcohol Syndrome

2. Use of epidemiologic data to confirm an association
   - Valproic acid identified as teratogen after case control study showed increased odds ratio for association of spina bifida if taken during 1st trimester of pregnancy

Teratogenicity

- Shepard’s Criteria
  - 1994, Thomas Shepard
  - Set of Seven Criteria for “proof” of human teratogenicity
Criteria 1, 2, and 3 = epidemiological approach

1. Proven exposure to the agent at one or more critical times during prenatal development
   - Case reports, case series, and epidemiologic studies of microcephaly in association with lab confirmed ZIKV infection
   - Infection during late first/early second trimester is associated with severe microcephaly and intracranial calcifications

2. Consistent findings by ≥ 2 high-quality epidemiologic studies
   - Partially met by the study in Brazil and another retrospective study from French Polynesia
   - Update: Colombian studies & US Zika Pregnancy Registry Results

3. Specific Defect or Syndrome
   - Congenital Zika Syndrome

Criteria 1, 3, and 4 = rare exposure-rare defect approach

4. Rare environmental exposure that is associated with a rare defect
   - Microcephaly is a rare defect with birth prevalence of about 6 cases per 10,000 live births in the US (birth-defects surveillance systems US)
   - ZIKV is a rare exposure for women who are traveling to other countries from the US

Criteria 5, 6, and 7 are helpful but not essential

5. Teratogenicity in experimental animals
   - 3 studies peripherally inoculated pregnant mice with resulting injury to CNS cells

6. Association should make biologic sense
   - Similar to prenatal infection with other viral teratogens (CMV, rubella virus)
   - ZIKV has been shown to be neurotropic in animal models
   - Evidence of ZIKV in fetal brain tissue with microcephaly

7. Proof in an experimental system that the agent acts in an unaltered state
   - Does not apply to infectious agents
Conclusion

- This review concluded that a "causal relationship existed between prenatal Zika virus infection and microcephaly and other serious brain anomalies."
- Absence of an alternative explanation
  - Brazil
  - Retrospectively in French Polynesia
    - 1% increase in microcephaly = 50 times increase from estimated baseline prevalence
  - Update: Studies from Colombia and the United States

Historical Correlation

- "The last time an infectious pathogen, rubella virus, caused an epidemic of congenital defects was more than 50 years ago."

Article 3

Retrospective Study from June 2015-May 2016

*Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally*
Study Population

- North Eastern Brazil in the Instituto de Pesquisa in Campina Grande State Paraiba (IPESQ)
- June 2015-May 2016 438 patients were referred:
  1. Pregnancy with rash
  2. Fetal CNS abnormalities on prenatal ultrasound
  3. Postnatal microcephaly or other CNS malformation thought to be due to Zika infection

Group 1: 384
  1. Pregnant women with history of rash
  2. CNS abnormality on US

Group 2: 47
  1. Neonates with postnatal microcephaly (Head circumference <32.5 cm) or other malformations

- 94 did not return for imaging to IPESQ/ no postnatal imaging
- 41 without CNS abnormality identified
- 1 dx with Trisomy 18
- 1 proven ZIKV but died without postnatal imaging
- **212 pregnancies ongoing**

Exclusion Criteria

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>94 did not return for imaging to IPESQ/ no postnatal imaging</td>
<td>26 did not return for imaging/ no postnatal images for review</td>
</tr>
<tr>
<td>41 without CNS abnormality identified</td>
<td>8 no <strong>calcifications</strong> suggestive of ZIKV</td>
</tr>
<tr>
<td>1 dx with Trisomy 18</td>
<td>Initially any normal head circumference was an exclusion criteria</td>
</tr>
<tr>
<td>1 proven ZIKV but died without postnatal imaging</td>
<td></td>
</tr>
</tbody>
</table>

Microcephaly

- -2 standard deviations below the mean for both boys and girls at term ~ 32.5 cm
- World Health Organization Criteria
- International Fetal and Newborn Growth Consortium for the 21st Century
Revised Criteria

- Initially there was an exclusion criteria for head circumference > 32.5 cm, however this was changed after imaging review showed normal head circumferences with:
  - Severe ventriculomegaly (due to hydrocephalus)
  - Calcifications

Cohort

- Confirmed Zika N=17 (includes set of twins)
  - Rash present in the first trimester in 81% (13 of 16 women)
- PCR and/or antibodies (IgM) = Confirmation of infection
  - 10 neonates with positive amniotic fluid
  - 7 positive in cord blood
  - 3 positive brain tissue during autopsy
  - Placenta in 1 neonate
- Presumed N=28 (Postnatal Suspicion Group)
  - Rash present in first trimester in 78% (22 of 28 women)

Rule out other causes

- All Tested Negative For:
  - Dengue and Chikungunya viruses
- TORCH Infection
  - Toxoplasmosis
  - Syphilis
  - Varicella-Zoster
  - CMV
  - Herpes
  - HIV
TORCH infections classically have periventricular calcifications.

**Other Findings**

- **Skull Abnormalities**
  - Collapsed shape, sloping forehead, overriding bones, cupped/everted sutures
    - Hypothesized as result of ventriculomegaly creating a larger head size with later decompression
    - Developing small brain
    - Cerebral atrophy
  - Redundant Cranial Skin Folds
    - Head and skin continue to grow while the size of the brain regressed
Axial bone window CT images at 37 weeks in a neonate with confirmed Zika infection

- Microcephaly with cerebral atrophy
- Ventriculomegaly
- Abnormal skull shape with some eversion of the bones at the sutures
- Calcifications in the subcortical white matter at the gray matter-white matter interface and periventricular

Sagittal fetal MR images at 36 weeks gestation

- Twin Gestation with maternal rash at 9 weeks of gestation with confirmed Zika infection.
- Severe microcephaly with profound frontal lobe hypoplasia
- Atrophic spinal cord
- Redundant skin in occipital region

Surface reconstruction postnatal CT images 1 week after delivery at 38 weeks gestation

Coronal MR images

- Hypoplasia of the corpus callosum
- Calcifications in the subcortical white matter at the gray-white matter junction and periventricular

Postnatal Axial CT images 1 week after delivery at 38 weeks gestation
Other Abnormalities

• Arthrogryposis

Calcifications in the subcortical region, thalamus, basal ganglia

5 month old male with head circumference 38 cm at birth with presumed ZIKV infection
1 of 3 neonates in the cohort that had a normal head circumference at birth due to severe ventriculomegaly
"This is an example of how ZIKV infection can be missed if only newborns with microcephaly are assessed"

November 3, 2016

Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians

• 5 features of Congenital Zika Syndrome that differentiate from other TORCH infections
  o Severe microcephaly with partially collapsed skull
  o Thin cerebral cortices with subcortical calcifications
  o Macular scarring and retinal mottling
  o Congenital Contractures
  o Marked early hypertonia with symptoms of extrapyramidal involvement
Macular Staining

Optic nerve hypoplasia with double-ring sign

Figure 1: Wide-angle fundus image (Nestam®) of the right eye of infant number 8 showing an optic disc hypoplasia with double-ring sign associated with a sharply demarcated choroidal shunt on the macula.

Placental Invasion

February 2017

Biochemistry

Cell Stem Cell

Zika Virus NS4A and NS4B Proteins Deregulate Akt-mTOR Signaling in Human Fetal Neural Stem Cells to Inhibit Neurogenesis and Induce Autophagy

Published:
August 11, 2016
Expression of either NS4A or NS4B reduced Akt phosphorylation of mTOR under normal conditions.

Results suggest that ZIKV NS4A and NS4B inhibit Akt-mTOR signaling pathway, impeding neurogenesis of fetal neural stem cells and increases autophagy (infectivity).

Reduced mTOR activity = Induction of Autophagy and increases ZIKV proliferation and infectivity.

13 Brazilian infants without microcephaly at birth, but + congenital Zika infection
- IgM in blood or CSF
- 3 with redundant scalp skin
- 1 with arthrogryposis

13/13 infants head growth deceleration as early as 5 months
- 11/13 infants developed microcephaly postnatally
- Hypertonia, hemiparesis, dyskinesia, dysphagia, seizures, and persistence of primitive reflexes

A. Newborn with no discernable anomalies including no craniofacial disproportion and normal limbs.
B. Same infant at 11 months with head circumference at almost 3 standard deviations (~2.89) below the mean but no apparent craniofacial anomalies.
C. Enlarged lateral ventricles

D. Corticomedullary calcifications

E. T2-weighted image. Slight irregularities of the inner cortical surfaces of the frontal lobes (black arrows), consistent with polymicrogyria.

**Significance**

- Evidence that infants with prenatal exposure to ZIKV who do not exhibit microcephaly at birth does not exclude congenital Zika related birth defects
- Supports comprehensive medical and developmental follow up for these infants
- Supports early neuroimaging for infants with supporting evidence of congenital infection, but normal head circumference

**ZIKV Birth Defects in the US**

**USZPR results Dec. 1, 2015-Dec. 27, 2016**

- CDC published on April 4th, 2017 updated results of the United States Zika Pregnancy Registry (USZPR)
- 2 ZIKV birth defect categories:
  - Brain abnormalities and/or microcephaly regardless of the presence of additional birth defects
  - Neural tube defects, other early brain malformations, eye abnormalities, and other consequences of central nervous system dysfunction with microcephaly
**ZIKV Birth Defects in the US**
USZPR results Dec. 1, 2015-Dec. 27, 2016

- 51/972 (5%) of infants had ZIKV-associated birth defects with probable recent ZIKV infection
- 24/250 (10%) of infants had ZIKV-associated birth defects with laboratory-confirmed ZIKV infection
  - 18 (75%), had brain abnormalities/microcephaly
- 15% of those with confirmed ZIKV and birth defects were infected in the first trimester

**Reporting**

- **U.S Zika Pregnancy Registry**
  - Pregnant women with positive laboratory testing whether symptomatic or asymptomatic and their infants
  - Results from December 2015-March 2018
    - 2,360 completed pregnancies
    - 116 liveborn infants had Zika-associated birth defects
      - 9 pregnancy losses with defects
- **State Based Birth Defect Surveillance System**
  - Any birth defects found in ZIKV + infants
- **Any persons with laboratory evidence of Zika virus**
  - Report to state/local health departments
ZIKV and Guillain-Barré Syndrome (GBS)

Guillain–Barré Syndrome Associated with Zika Virus Infection in Colombia

* January-March 2016 at university hospitals in Colombia
* Patients were examined by internal medicine and neurology specialists
* ZIKV infection was stratified as
  - **Definite**: + RT-PCR (blood, urine, CSF)
  - **Probable**: + Anti flavivirus antibody ELISA (blood and/or CSF), but negative RT-PCR
  - **Suspected**: Presence of clinical features without testing

![Chart showing cases of ZIKV infection and Guillain-Barré syndrome in Colombia]
Results

- 66% met criteria for Guillain-Barré syndrome
- Results: ZIKV as infectious trigger for GBS is supported

ZikV Systematic Review from PLOS

Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain-Barré Syndrome: Systematic Review


Published: January 3, 2017 • http://dx.doi.org/10.1371/journal.pmed.1002303

ZIKV Systematic Review

- Analyzed 72 studies addressing ZIKV causality of congenital brain abnormalities
- Analyzed 36 studies addressing ZIKV causality of triggering GBS
- Results: Found sufficient evidence to conclude that ZIKV is a cause of congenital abnormalities and is a trigger of GBS
Who do we test:
- Infants with abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal Zika test results.
- Infants born to mothers with laboratory evidence of ZIKV infection during pregnancy
  - All symptomatic pregnant women are eligible for Zika testing.
  - Asymptomatic pregnant women with possible exposure up to 12 weeks after the exposure with PCR.

Local Testing for Children
- Children locally without travel history who have 3 of 4 symptoms:
  - Fever
  - Rash
  - Conjunctivitis
  - Arthralgia
- High index of suspicion in children with travel history who have fever + 1 other symptom
  - Border towns such as Brownsville are considered a positive travel history

How Do We Test Infants?
- Test serum, urine, and/or CSF:
  - ZIKV rRT-PCR (real-time reverse transcription-polymerase chain reaction)
  - Dengue virus and Chikungunya PCR and IgM (ELISA)
- Test mother if not already tested
- Consider histopathologic evaluation of the placenta and umbilical cord
  - ZIKV immunohistochemical staining
  - ZIKV RT-PCR
Symptomatic Children/Adults

- **Onset < 1-4 Days**
  - Zika Serum RT-PCR and Urine RT-PCR

- **Onset 4-7 Days**
  - Zika Serum RT-PCR Zika, Urine RT-PCR, & Serum IgM

- **Onset 7-14 Days**
  - Zika Serum IgM and Urine RT-PCR

- CSF PCR and IgM at any time if doing LP due to clinical concerns

- Serum PCR and IgM for Dengue and Chikungunya

- PCR for patients at risk of exposure

---

What is a + Test?

- ZIKV + PCR in any sample

- Serology:
  - + ZIKV IgM with confirmatory neutralizing antibody titers that are ≥ 10 fold higher than dengue virus

- Inconclusive Result:
  - ZIKV IgM with confirmatory neutralizing antibody titers that are ≤ 10 fold higher than dengue virus

---

Clinical Evaluation with Possible CZS

- **Physical Exam**
  - Head circumference, length, weight (Growth Curves)
  - Document dysmorphic features and contractures
  - Hepatosplenomegaly
  - Rash or other skin lesions

- **Head US**

- **Hearing Evaluation (ABR)** prior to discharge at birth hospital or within 1 month of birth

- **Ophthalmologic (retina) exam**
PE consistent with Congenital Zika Syndrome

- MRI/CT for abnormalities consistent with CZS
  - USZPR reported only 25% received
  - Pediatric Neurologist Referral
- Testing for other congenital infections
  - Syphilis, Toxoplasmosis, Rubella, CMV, HSV
  - Pediatric Infectious Disease Referral
- Lab evaluation
  - CBC, platelet count, liver function and enzymes (ALT, AST, Bilirubin)
- Consider genetic and other teratogenic causes based on congenital anomalies, exam, and imaging

Continued Inpatient Management

- Endocrinology
  - Hypothalamic/ Pituitary Dysfunction
- Pulmonology/ Speech Therapy
  - Aspiration Concerns
- Orthopedics/ Physical Therapy
  - Hypertonia/ Arthrogryposis

Long Term Follow Up

- Monthly check-ups for the first 6 months of life
- Evaluate:
  - Occipitofrontal circumference
  - Full physical exam with ophthalmological and neurological emphasis
  - Developmental Milestones
  - Routine immunizations
  - Additional hearing screen at 4-6 months
  - Thyroid Screening at 2 weeks and 3 months
  - Developmental Specialist and Early intervention therapies
    - Physical, Occupational, Speech Therapy
Treatment

- No antiviral treatment
- Supportive care
  - Should address specific medical and neurodevelopmental issues for infant’s particular needs
- Breastfeeding
  - ZIKV RNA has been detected in breast milk
  - No documented transmission
  - There have now been several documented cases of infection
  - Benefits outweigh risk of virus transmission

Vaccines

- Zika Purified Inactivated Virus (ZPIV) Vaccine
  - Phase I Clinical Trial at Walter Reed Army Institute of Research began November 2016
  - Inactivated whole Zika virus
- DNA Zika Vaccine
  - National Institute of Allergy and Infectious Diseases
  - Phase 2 Clinical Trials began in March 2017
- Both vaccines have been immunogenic and blocked Zika infection in primates

South Texas Congenital Zika Experience
Case Series

- 18 cases of possible ZIKV infection in pregnant women were identified by screening and testing of symptomatic patients living in Brownsville, TX, December 2016-May 2017 who presented for care at the Driscoll maternal fetal medicine clinic.
  - 12 women had PCR + results indicating laboratory evidence of ZIKV infection
    - 8 Serum
    - 3 Serum and Urine
    - 1 Placenta
  - 6 women with IgM +
  - Subsequent PRNT (plaque reduction neutralization test)
    - 1 with recent ZIKV infection
    - 5 with recent flavivirus infection
- 2 women had findings consistent with congenital Zika syndrome (CZS)

Case 1

- The first 4 months of pregnancy were spent in Matamoros, Mexico where prenatal ZIKV testing was negative
- Moved to Brownsville, TX where she established care at 28 weeks' gestation and was screened with ZIKV serum IgM and results were negative
- 36 weeks' gestation referred to MFM for fetal microcephaly

Prenatal transvaginal US (midsagittal plane) image at 37.2 weeks' gestation, showing microcephaly and calcifications at the gray matter—white matter junction. Head circumference was 251 mm (5 standard deviations below the mean value).
Case 1 (cont.)

- Based on the US results a repeat ZIKV IgM was performed and positive at 37 weeks’ gestation
- PRNT results were consistent with recent flavivirus infection (ZIKV & dengue PRNT titers > 1,280)
- Prenatal TORCH testing was negative
  - Toxoplasmosis, Rubella, CMV, HSV, HIV
- Cell-free fetal DNA screening was negative
- The infant was delivered at 39 weeks’ gestation

Craniofacial abnormalities present are mild narrow and laterally depressed frontal bone and mild retrognathia. Generalized pustular melanosis rash.

Microcephaly on the day of birth. Head circumference was 29 cm, which is 2.63 SDs below the mean value for term male newborns.
ZIKV testing was conducted on the first day of life
- ZIKV PCR serum, urine, and CSF (-)
- ZIKV IgM serum (+) / CSF IgM displaced by lab
- Placental RT-PCR for NS protein 5 gene (+)
- PRNT (cannot be done until 18 months of life)
- Dengue and Chikungunya PCR and IgM (-)
- Neonatal TORCH testing (--)
- Microarray and microcephaly gene panel (--)

Head US revealed calcifications in the parietal lobe and gyral abnormality
Case 2

- Patient lived in Brownsville with weekly travel to Matamoros, Mexico during the first few months of her pregnancy

- Screened at 23 weeks’ gestation by OBGYN via ZIKV serum PCR and was (+)

- 28 weeks’ gestation fetal US showed microcephaly and a referral to MFM was made
  - Head circumference of the fetus was 203 mm at 28 weeks’ gestation (4-5 SD below the mean value)

Axial computerized tomography image on day of life 3

Tranabdominal US image of the axial transthalamic plane at 37 weeks' gestation
Case 2 (cont.)

- Prenatal TORCH testing was negative
  - Toxoplasmosis, Rubella, CMV, HSV, HIV
- The infant was delivered at 39 weeks’ gestation

Day of life 1. Head circumference was 26.5 cm, which is 6.23 SD below the mean value for term females.

- Craniofacial disproportion with narrow and laterally depressed frontal bone is seen.
- Upper wrist contractures are present, more apparent on the right, with ulnar deviation.
Redundant scalp skin with multiple rugae.

Case 2 (cont.)

- ZIKV testing was conducted on the first day of life
  - ZIKV PCR serum, urine, and CSF (-)
  - ZIKV IgM serum (-) / CSF IgM displaced by lab
  - Dengue and Chikungunya PCR and IgM (-)
  - Neonatal TORCH testing (-)
  - Microarray and microcephaly gene panel (-)

- Head US could not be done due to the anterior fontanelle being too small

Sagittal T2 turbo spin echo MRI image on day of life one
Axial T2 turbo spin echo MRI on day of life 1

- Enlarged extra-axial spaces
- Smooth gyral pattern
- Large bilateral posterior parietal and occipital lobe parenchymal cysts

Testing
- Both neonates required orogastric tube feeding
- Both neonates passed:
  - Initial newborn hearing screens
  - Ophthalmologic exams
  - EEG
  - ECHO
  - Thyroid function testing
  - Complete blood count
  - Comprehensive metabolic panel

Discharge
- Case 1 was discharged on day 9 of life from the NICU
  - Discharge HC 30 cm, 3.16 SD below the mean
- Case 2 developed excessive irritability and was started on phenobarbital
  - Developed intermittent tremors and hypertonia
  - Discharged from NICU on day of life 27 with HC of 27 cm
    - 7.42 SD below the mean
What We Know

- ZIKV RNA can remain in serum for 75 days
- Neonates who are ZIKV+ need long term follow up and neuroimaging
- ZIKV is a cause of CZS and a trigger for GBS

What We DO NOT Know

- The length of persistence of IgM
- The long term progression of CZS
- Neurocognitive sequelae in older children with infection

Summary

- ZIKV infection during pregnancy can cause a spectrum of CZS that occurs in 1 of 10 pregnancies with confirmed infection
- There are no current treatments for ZIKV infection
  - There are no currently approved antivirals
  - There are no vaccines or immunoglobulin approved for immunoprophylaxis

Can an infant with prenatal exposure to the Zika virus and does not exhibit microcephaly at birth still have congenital Zika-related birth defects?

Yes

No
**Which of the following are possible congenital Zika-related birth defects?**

<table>
<thead>
<tr>
<th>Congenital Zika-related Birth Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly or brain abnormalities</td>
</tr>
<tr>
<td>Neural tube defects/other early brain malformations</td>
</tr>
<tr>
<td>Eye abnormalities without brain abnormality included in the first two categories</td>
</tr>
<tr>
<td>Joint contractures/Congenital sensorineural deafness</td>
</tr>
<tr>
<td>All of the above</td>
</tr>
</tbody>
</table>

**How do you test for Zika virus?**

<table>
<thead>
<tr>
<th>Test for Zika virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test serum, urine, and/or CSF for: ZIKV rRT-PCR, ZIKV IgM, Dengue virus and Chickungunya IgM</td>
</tr>
<tr>
<td>Test the mother if not already tested</td>
</tr>
<tr>
<td>Histopathologic evaluation of the placenta and umbilical cord</td>
</tr>
<tr>
<td>All of the above</td>
</tr>
</tbody>
</table>

**Treatment for Zika virus includes all except?**

<table>
<thead>
<tr>
<th>Treatment for Zika virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral therapy</td>
</tr>
<tr>
<td>Supportive care</td>
</tr>
<tr>
<td>Breastfeeding</td>
</tr>
<tr>
<td>All are appropriate treatment for Zika virus</td>
</tr>
</tbody>
</table>
References