Module Five

Congenital Abnormalities
Clinical Criteria

Liveborn infant with congenital microcephaly, or intracranial calcifications, or structural brain or eye abnormalities, or other congenital central nervous system-related abnormalities not explained by another etiology.

*Called Zika Virus Syndrome in some places and Zika Virus Disease others

CASE CLASSIFICATION: PROBABLE

A neonate meets clinical criteria for congenital disease; AND
The neonate’s mother has an epidemiologic linkage or meets laboratory criteria for recent ZIKV or flavivirus infection; AND
The neonate has laboratory evidence of ZIKV or flavivirus infection by:

• Positive ZIKV IgM antibody test of serum or CSF collected within 2 days of birth; AND
  – positive neutralizing antibody titers against ZIKV and dengue or other flaviviruses endemic to the region where exposure occurred; OR
  – negative dengue virus IgM antibody test and no neutralizing antibody testing performed.
CASE CLASSIFICATION: CONFIRMED

A neonate meets the clinical criteria for congenital disease AND meets one of the following laboratory criteria:

• ZIKV detection by culture, viral antigen, or viral RNA in fetal tissue, umbilical cord blood, or amniotic fluid; or neonatal serum, CSF, or urine collected within 2 days of birth; OR

• Positive ZIKV IgM antibody test of umbilical cord blood, neonatal serum or CSF collected within 2 days of birth with positive ZIKV neutralizing antibody titers and negative neutralizing antibody titers against dengue or other flaviviruses endemic to the region where exposure occurred.

Microcephaly is a very specific diagnosis, and typically unusual as an isolated finding: initially seen in *newborns*
- On ultrasound, typically defined as *HC < 3rd %ile* for GA

Microcephaly became an *early trigger* to search for Zika association, but spectrum of disease became apparent
- Microcephaly can occur as a result of a *fetal brain disruption sequence*: this appears to be pathology of Zika infection
SEVERE MICROCEPHALY WITH PARTIALLY COLLAPSED SKULL

Microcephaly is defined as a head circumference measurement that is smaller than a certain value for babies of the same age and sex.
• The measurement value for microcephaly is usually less than 2 standard deviations (SDs) below the average.
• The measurement value also may be designated as less than the 3rd percentile.

Source: https://www.cdc.gov/ncbddd/birthdefects/microcephaly.html
Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?
Fetal Brain Anomalies

- Microcephaly
- Hydrocephalus/hydranencephaly
- Absent structures: (CC, pons, cerebellar vermis)
- Neuronal migration disorders (lissencephaly)
- Fetal brain disruption sequence
- Cerebral calcifications
- Brain asymmetry
Zika Virus Infection in Pregnant Women in Rio de Janeiro


ABSTRACT

BACKGROUND
Zika virus (ZIKV) has been linked to central nervous system malformations in fetuses. To characterize the spectrum of ZIKV disease in pregnant women and infants, we followed patients in Rio de Janeiro to describe clinical manifestations in mothers and repercussions of acute ZIKV infection in infants.

METHODS
We enrolled pregnant women in whom a rash had developed within the previous 5 days and tested blood and urine specimens for ZIKV by reverse-transcriptase–polymerase-chain-reaction assays. We followed women prospectively to obtain data on pregnancy and infant outcomes.

RESULTS
A total of 345 women were enrolled from September 2015 through May 2016; of these, 182 women (52.8%) tested positive for ZIKV in blood, urine, or both. The timing of acute ZIKV

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A preliminary version of this article was published on March 4, 2016, at NEJM.org.
STUDY RESULTS SUMMARY

• Final report updates preliminary data on ZKV infection among pregnant women in Rio de Janeiro
  – Expands study cohort from 88 to 134 symptomatic women with confirmed ZKV infection
  – Fetal loss and OB complication rates and similar for Zika (+) and (-) groups (~7% and 35% respectively)
  – ZKV (+) women 10X more likely to have c/s for fetal distress and 4X more likely to need neo critical care after birth
  – Microcephaly in 4 infants: infections at 8, 12, 30, 38 weeks
  – Overall, 49/117 (42%) liveborn ZKV-exposed infants had abnormal findings in 1st month of life [5% in ZKV(-): p< 0.001]

• Adverse outcomes seen regardless of trimester of infx
  – 55% risk if maternal infx in 1st, 52% if in 2nd, 29% if in 3rd
KNOWN ABNORMALITIES UNIQUE TO ZIKA VIRUS SYNDROME

‘CHARACTERIZING THE PATTERN OF ANOMALIES IN CONGENITAL ZIKA SYNDROME FOR PEDIATRIC CLINICIANS’
JAMA PEDIATRICS, OCTOBER 2016

- Severe microcephaly with partially collapsed skull
- Thin cerebral cortices with subcortical calcifications
- Macular scarring and focal pigmentary retinal mottling
- Congenital contractures
- Marked early hypertonia and symptoms of extrapyramidal involvement

Source: http://jamanetwork.com/journals/jamapediatrics/fullarticle/2579543
Fig 3 Severe microcephaly.
VENTRICULAR CALCIFICATION OR OTHER CENTRAL NERVOUS SYSTEM LESIONS
CT Scans Reveal Extensive Abnormalities

23 infants with microcephaly in Pernambuco, Brazil

- Intracranial calcifications
- Global cortical hypogyration
- Ventriculomegaly
- Global cerebellar hypoplasia

Source: Hazin et al, NEJM April 6, 2016
OPHTHO CRITERIA FOR CZS

• First ophthalmological examination has to be performed within 30 days of birth.

• SIGNS: Focal pigment mottling of the retina and circular lesions of chorioretinal atrophy including the macula, along with optic nerve abnormalities
  – Identified in 30% of newborns with microcephaly (Frietas et al, JAMA Ophtho 2/16)

• UNIQUE CHORIORETINAL ATROPHY
MACULAR SCARRING AND FOCAL PIGMENTARY RETINAL MOTTLING

A  Right eye

B  Left eye

Source: [http://jamanetwork.com/journals/jamaophthalmology/fullarticle/2491896](http://jamanetwork.com/journals/jamaophthalmology/fullarticle/2491896)
Arthrogryposis multiplex congenita (AMC), or simply arthrogryposis, describes **congenital joint contractures** in two or more areas of the body. It derives its name from Greek, literally meaning "curving of joints" (arthron, "joint"; grūpōsis, late Latin form of late Greek grūpōsis, "hooking").
CONGENITAL CONTRACTURES (ARTHROGRYPOSIS)

(A) Contracture in flexion of knee;
(B) Hyperextension of knee (knee dislocation);
(C) Clubfeet;
(D) Deformities in 2nd, 3rd,
and 4th fingers;
(E) Joint contractures in legs
and arms, without involvement of trunk

Source: http://www.bmj.com/content/354/bmj.i3899
MARKED EARLY HYPERTONIA AND SYMPTOMS OF EXTRAPYRAMIDAL INVOLVEMENT

• Loss of upper motor and alpha motor neurons can result in hypertonia, or increase in muscle tone.
• Increased resistance is apparent when the arms and legs are extended.
• Hyperextension of the back and tightly clenched fists are often seen.

Sources: [http://neuroscience.uth.tmc.edu/s3/chapter06.html](http://neuroscience.uth.tmc.edu/s3/chapter06.html) and [http://www.slideshare.net/peso88888/neonatal-examination-45813957](http://www.slideshare.net/peso88888/neonatal-examination-45813957)
Other Known Abnormalities Associated with Zika Virus Syndrome

- Strabismus
- Cutis Gyrate
- Hypotonia
- Hyperreflexia
- Glaucoma
- Irritability
- Seizures
**Other Ocular Findings: Strabismus**

Increased occurrence of strabismus (crossed eyes). 14% in babies with congenital Zika virus syndrome versus 3-5% in the general population.

Source: Study by Marcia Tartarella, MD, PhD, et al, under review
Cutis verticis gyrata (CVG) is a descriptive term for a condition of the scalp manifesting as convoluted folds and furrows formed from thickened skin of the scalp resembling cerebriform pattern.

HYPOTONIA

Hypotonia (decreased muscle tone)

Source: https://englishforphysio.wordpress.com/tag/spasticity/
Hyperreflexia is defined as overactive or overresponsive reflexes. Examples of this can include twitching or spastic tendencies, which are indicative of upper motor neuron disease as well as the lessening or loss of control ordinarily exerted by higher brain centers of lower neural pathways (disinhibition).

Source: https://en.wikipedia.org/wiki/Hyperreflexia
Study in Brazil, *Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study* (British Medical Journal, April 2016), shows evidence of seizures in CT and MRI scans of infants born with congenital Zika syndrome.
SUMMARY: ZIKA- ASSOCIATED ADVERSE PREGNANCY OUTCOMES

- Fetal loss/miscarriage, stillbirth
- Fetal growth abnormalities
  - Microcephaly
  - Ventriculomegaly
  - Intracranial calcifications
- Fetal brain anomalies
- Eye abnormalities
- Neurologic
  - Hypertonia
  - Arthrogryposis
  - Seizures
  - Neurobehavioral anomalies
WHAT’S NEXT?

Treatment Options