Neuroimaging Findings in Congenital Zika Syndrome

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Disclosure
• We have nothing to disclose
• No relevant financial relations interfering with our presentation

Zika virus
• Detected first in 1947 in the Zika forest in Uganda
• Mosquito borne flavivirus
• Transmitted primarily by Aedes aegypti mosquitoes
• Zika virus infection: subclinical (up to 80%) or mild illness causing fever, conjunctivitis, arthralgia, myalgia, and rash; exception: Guillain-Barré

Zika virus and microcephaly
• March 2015, north east Brazil: outbreak of Zika virus infection
• October 2015, Pernambuco State: unexplained increase in cases of congenital microcephaly
• Prevalence of congenital microcephaly increased by a factor of 20
• In 2015: 1248 new suspected cases ➔ prevalence 99.7/100 000 live births

SPECIAL REPORT
Zika Virus and Birth Defects — Reviewing the Evidence for Causality
Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle B. Peterson, M.D., M.P.H.

On the basis of this review, we conclude that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies

Congenital Zika syndrome
• Many fetuses and infants with congenital Zika virus infection have a typical phenotype:
  – Microcephaly/abnormal cranial morphology
  – Intracranial calcifications
  – Other brain anomalies
  – Eye abnormalities (inconsistent)
  – Redundant scalp skin (inconsistent)
  – Arthrogryposis (inconsistent)
Cranial morphology

- Fetal brain disruption sequence:
  - Severe microcephaly (< 3 SD mean)
  - Cranio-facial disproportion
  - Redundant scalp skin (rugae)
- Most likely due to small brain and decrease in intracranial pressure
- Nonspecific, but common in congenital Zika syndrome

Brain findings in congenital Zika syndrome

1. Intracranial calcifications
2. Ventriculomegaly
3. Cortical thinning with abnormal gyral pattern
4. Hypoplasia or absence of the corpus callosum
5. Abnormal myelination
6. Cerebellar or vermis hypoplasia

Intracranial calcifications

- Most common intracranial finding
- Present in almost all reported patients
- Subcortical location
- Mostly punctate/band-like distribution

Intracranial calcifications may be detected by prenatal ultrasound from the end of the first trimester.
Ventriculomegaly

- Present in 85-100% of children
- Mostly moderate to severe
- Typically entire ventricular system
- Septations in lateral ventricle: 10-30%
- Subependymal cysts

Subependymal cysts in a few patients

Septations in the lateral ventricle: 10-30%

Ventriculomegaly may be detected by prenatal ultrasound or MRI from the end of the first trimester

Cortical abnormalities

- Present in 95-100% of patients
- Mostly diffuse brain involvement
- Type of cortical abnormality:
  - Polymicrogyria: 57%
  - Lissencephaly: 18%
  - Not specified abnormality: 25%

Cortical thinning with polymicrogyria
Cortical abnormalities

- Cortical thinning with polymicrogyria
  - Almost completely smooth cerebral surface with a thick cortex compatible with lissencephaly

Cortical abnormalities

- Abnormal cortical gyration may be seen on fetal MRI
  - Abnormal white matter myelination
    - 88-100% of patients
    - Delayed myelination or dysmyelination
  - Cerebellar + brainstem hypoplasia
    - 27-82% of children
    - Vermis hypoplasia: 59-68%
    - Cerebellar hypoplasia: 39-82%
    - Brainstem hypoplasia: 21-70%, mostly affecting the pons

Callosal abnormalities

- 75-94% of patients
- Mostly thin, dysgenetic, and hypoplastic or even absent
- May be associated with abnormal rotation of the hippocampi and thickened fornices
Cerebellar + brainstem hypoplasia

Hypoplasia of cerebellum + pons on fetal MRI
Reliable assessment after 24 weeks of gestation

Spinal cord atrophy

- Thinning of the spinal cord + small ventral roots
- Association with arthrogryposis of neurogenic etiology

Ischemic stroke

- In one child: chronic encephalomalacic changes from ischemic stroke in the vascular territory of the left MCA
- Possible associated vasculitis?

Brain anomalies in congenital Zika syndrome

- Most likely due to direct cellular injury → ZIKV RNA and live virus identified in brain tissue
- Neural progenitor cells = primary target of ZIKV
- Postmigratory neurons = apoptotic
  → Suggest disruption of existing immature neurons + decreased proliferation and impaired migration due to loss of progenitor cells

Disruption versus Malformation

- **Disruption** = Congenital anomaly due to the breakdown of a body structure that had a normal developmental potential
- **Malformation** = Congenital anomaly due to an alteration of the primary developmental program caused by a genetic defect

Prenatal disruptions

- Ischemia/stroke
- Diffuse hypoxia (placental insufficiency)
  - Hemorrhage
  - Infections
  - Teratogens

Stroke
CMV
Prenatal disruptions

- **Timing** of the “event” is key feature
- Identical “(disruptive) events” can result in **spectrum** of fetal pathologies

Differential diagnosis

1. Congenital TORCH infections
2. Aicardi-Goutières syndrome
3. Pseudo-TORCH syndrome
4. Mutations in JAM3 and NDE1 genes

Differential diagnosis

- Congenital CMV vs congenital Zika

<table>
<thead>
<tr>
<th>Congenital CMV infection</th>
<th>Congenital Zika syndrome</th>
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<tbody>
<tr>
<td>Location of calcifications = <strong>PERIVENTRICULAR</strong></td>
<td>Location of calcifications = <strong>CORTICOMETULLARY JUNCTION</strong></td>
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<tr>
<td>Temporal cysts</td>
<td>More commonly basal ganglia + thalamic calcifications</td>
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Many questions to be answered

- Are we looking at the tip of the iceberg?
- What about the normo-cephalic children?
- How often is there maternal infection without fetal affection?
- Is timing and severity of infection relevant?
- Are there “typical” imaging patterns?
- Is Zika alone causative or does it require a combination of infectious agents (Zika + Dengue)?
- What is the best imaging modality?
- Which imaging modality can serve as a screening tool?

Take-home messages

1. Neuroimaging findings in congenital Zika syndrome = **cortico-medullary calcifications**, ventriculomegaly, thin cortex with abnormal gyral pattern (polymicrogyria), abnormal white matter myelination, cerebellar/pontine hypoplasia
2. Cranial morphology = microcephaly, fetal brain disruption sequence
3. DD with other congenital infections (CMV): location of calcifications

Thank you