"Why Is Our Baby’s Head Small?"

The Pathogenesis of Microcephaly Resulting From Zika Virus and Other Congenital Infections

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The Authors Have No Conflicts of Interest to Disclose
Questions to Try to Answer About Congenital Microcephaly

• Why do some women get infected with the responsible pathogens?
• Why are their pathogen loads high enough to cross the placenta and infect their fetus?
• Why are some fetuses merely infected while others are afflicted*?
• What determines the pattern and degree of affliction?

* Congenitally infected infants who demonstrate stigmata at birth
## Major Pathogens Associated with Congenital Microcephaly

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Risk of Affliction with Primary Maternal Infection (%)*</th>
<th>% of Afflicted Infants with Microcephaly*</th>
<th>Sexual Transmission</th>
<th>Vaccine Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zika Virus</td>
<td>40</td>
<td>20</td>
<td>Yes</td>
<td>In clinical trials</td>
</tr>
<tr>
<td>CMV</td>
<td>15</td>
<td>50</td>
<td>Yes</td>
<td>Not in use</td>
</tr>
<tr>
<td>Rubella Virus</td>
<td>50</td>
<td>10</td>
<td>No</td>
<td>Routine</td>
</tr>
<tr>
<td>HSV</td>
<td>1</td>
<td>&lt;3</td>
<td>Yes</td>
<td>In clinical trials</td>
</tr>
<tr>
<td>HVZ</td>
<td>2</td>
<td>rare</td>
<td>No</td>
<td>Routine</td>
</tr>
<tr>
<td>Toxoplasma</td>
<td>10</td>
<td>5</td>
<td>No</td>
<td>None available</td>
</tr>
</tbody>
</table>

*Best average estimates of published data at this time*
### Reported Pathologic Findings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Zika virus&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CMV&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Rubella virus&lt;sup&gt;c&lt;/sup&gt;</th>
<th>HSV&lt;sup&gt;b&lt;/sup&gt;</th>
<th>VZV&lt;sup&gt;b&lt;/sup&gt;</th>
<th>T. gondii&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intrauterine growth retardation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CNS calcifications</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chorioretinal inflammation, atrophy, or scars</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hydrocephalus, hydranencephaly or ventriculomegaly</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Malformed gyri</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cortical dysplasia</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebellar hypoplasia or aplasia</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Encephalitis or meningoencephalitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Microphthalmia</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
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<tr>
<td>Optic nerve atrophy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Cardiac anomalies</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Hepatic dysfunction</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup> ss+RNA flavivirus, <sup>b</sup> dsDNA herpesvirus, <sup>c</sup> ss+RNA togavirus, <sup>d</sup> intracellular protozoan

√ Most characteristic findings in TORCH afflicted infants
Zika Virus Characteristics

• Epidemiology: High attack rate at 70% (data from Yap Island)
• Transmission: *Aedes aegypti* mosquito & sexually
• Primary maternal infection resulting in congenital Zika affliction: 1\textsuperscript{st} and 2\textsuperscript{nd} trimester
• Not neurotropic in most individuals; some G-B Syndrome
• Major manifestations
  - Maternal: Asymptomatic disease in 80%; rash, headache, arthralgia, myalgia, *conjunctivitis*, and low-grade fever
  - Congenital: Microcephaly, CNS calcifications and other malformations, intrauterine growth retardation (IUGR), sensorineural hearing loss, chorioretinitis and other eye abnormalities, seizures, developmental delay
Cytomegalovirus Characteristics

- Epidemiology: Very common infection worldwide; most common congenital infection in the US
- Transmission: Sexually and via oral secretions
- Primary maternal infection resulting in congenital CMV: 1st or 2nd trimester; however
  - Fetal infection can occur as reactivation or reinfection in seropositive mothers
- Not neurotropic in immune competent individuals
- Major manifestations
  - Maternal: Generally asymptomatic; mild flu-like symptoms
  - Congenital: Microcephaly, CNS calcifications and other CNS malformations, IUGR, sensorineural hearing loss, chorioretinitis and other eye abnormalities, seizures, developmental delay; petechiae and jaundice indicating fetal dissemination
Characteristic Chorioretinitis Secondary to Congenital CMV
Unilateral Microphthalmia
in Child With
Congenital
CMV
“Burst Suppression” Silent Seizures in Congenital CMV (Same Side as Microphthalmia)
Rubella Virus Characteristics

- Epidemiology: Moderately high attack rate prior to vaccine availability now rare
- Transmission: Respiratory
- 1st trimester maternal infection results in congenital affliction in a remarkable 50% of infants
- Neurotropic manifestations: Uncommon, include mild encephalitis
- Major manifestations
  - Maternal: Generally mild self limited symptoms, with fever, rash, and adenopathy
  - Congenital: Microcephaly, CNS calcifications and other CNS abnormalities, IUGR, sensorineural hearing loss, eye abnormalities, developmental delay, petechiae, and jaundice; **Greg’s classic triad from 1941: Deafness, cataracts, cardiac abnormalities**
Herpes Simplex Virus Characteristics

- Epidemiology: Common infection in women, mostly recurrent;
- Transmission: Moderately infectious with sexual or close skin or mucous membrane contact
- Primary maternal infection resulting in congenital HSV is rare but occurs in the: 1st or 2nd trimester
- Neurotropic manifestations: Encephalitis and latency in neural tissues
- Major manifestations
  - Maternal: Localized genital lesions, disseminated cutaneous or multi-organ (sometimes fatal) dissemination
  - Congenital: Evidence of necrotizing CNS, pulmonary, hepatic dissemination and DIC; as well as rare microcephaly
Herpes Varicella-Zoster Virus Characteristics

• Epidemiology: The incidence of primary maternal disease is low: Most mothers were seropositive historically, because of the highly infectious nature of childhood disease And, more recently, because of the widespread use of the vaccine

• Transmission: Aerosol of respiratory secretions and fomite contact

• Primary maternal infection resulting in congenital HVZ: 1st or 2nd trimester

• Neurotropic manifestations: Encephalitis, Zoster, and latency in neural tissue

• Major manifestations

  Maternal: Similar to disease in children and others

  Congenital: Cicatricial skin scarring, limb hypoplasia, CNS malformations, eye abnormalities, and very rare microcephaly
Cicatricial Shin Lesions in Congenital HVZ affliction
Toxoplasma Characteristics

• Epidemiology: Incidence is dependent on geography and culture; a major cause of adolescent blindness via reactivation of silent congenital infection manifest with chorioretinitis

• Transmission: Generally via cat feces (e.g. changing cat litter boxes) or by eating raw meat (especially lamb)

• Primary maternal infection resulting in congenital toxoplasmosis: 1st or 2nd trimester

• The organisms seem to have a broad tropism for CNS tissue

• Major manifestations
  
  Maternal: Generally asymptomatic or unrecognized

  Congenital: Microcephaly, CNS calcifications and other CNS abnormalities, IUGR, sensorineural hearing loss, chorioretinitis and other eye abnormalities, seizures, developmental delay, jaundice and anemia
Characteristic Chorioretinitis Secondary to Toxoplasma Infection
Depression of Specific and Non-specific Cell Mediated Immunity During Pregnancy

(Frenkel, L.D, et.al. Presented at the Conjoint Meeting on Infectious Diseases, Montreal, Canada, December, 1983)
Specific Immunopathogenic Observations

- Reactivation and reinfection can be associated with congenital CMV affliction in seropositive pregnant women
- Reactivation can be associated with delayed blindness in congenital toxoplasmosis
- Persistent CMV and rubella virus shedding in congenitally infected infants and their mothers is reflective of decreased and delayed viral specific T cell mediated immunity
The Pathology Of Microcephaly (1)

- **Intracellular pathogens** that are **tropic for human fetal CNS tissue**
- Cause neuron infection resulting in death, decreased replication, and abnormal migration
- This causes decreased brain tissue mass and volume reflected in **microcephaly**
- Common findings
  - Increased intracranial fluid
  - Lymphohistiocytic inflammation of brain and/or meninges
    - Which yields cerebral cortical thinning, cerebral schizencephaly, pachygyria, and/or lissencephaly; and/or hypoplasia or aplasia of cerebellum (e.g. cerebellar vermis aplasia) and/or corpus callosum
The Pathology Of Microcephaly (2)

- The inflammation and decreased brain matter are associated with ventriculomegaly, hydrocephalus and hydranencephaly.
- As the fluid levels and brain mass recede there is collapse of the cranial vault, overriding of the cranial bones, flattening of the cranium and redundant scalp skin.

The Pathology Of Microcephaly (3)

- The differential neuropathology of microcephaly associated with these pathogens is not clear at this time.
- However, the kinetics of CNS tissue destruction may be reflected in the pattern and character of microcephaly (e.g. Zika virus destruction is more severe and rapid than is seen with CMV and other pathogens).
Hypothesis To Explain Congenital Affliction

- Pregnancy leads to a generalized down-regulation of T cell mediated immunity to help preserve the fetal graft.
- Multiple, less understood, factors including primary maternal infection and a more profound immune suppression than is seen in normal pregnancy allow for invasion of maternal circulation and determine the pathogen load delivered to the placenta.
- Failure of maternal-fetal barriers allows pathogen dissemination to multiple susceptible developing organs in the fetus.
The timing of maternal infection (early gestation is when important embryonic events are occurring), and cellular tropism, together, determine the characteristics and degree of affliction.

The pathology of microcephaly is similar regardless of causal pathogen but implies maternal infection early in gestation.

The final step in congenital affliction is chronic destructive inflammation thought to be the result of down-regulation of fetal immune defenses in the face of up-regulation of fetal innate immune responses that promote inflammation.
# Microcephaly and Flavi/Arbo Viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Documented Intrauterine Transmission (Number of cases/Number studied)</th>
<th>Exposure</th>
<th>Method of Fetal Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dengue</strong></td>
<td>5/34 (15%) disseminated disease; no microcephaly</td>
<td>3rd trimester</td>
<td>Specific IgM Ab Viral isolation</td>
</tr>
<tr>
<td><strong>Chikungunya</strong></td>
<td>38/7504 (0.5%) CNS lesions on MRI, 5 (0.07%) with microcephaly, and disseminated disease</td>
<td>Variable</td>
<td>RT PCR Specific IgM antibody</td>
</tr>
<tr>
<td><strong>West Nile</strong></td>
<td>1 CNS lesions on MRI, chorioretnitis</td>
<td>Early 3rd trimester</td>
<td>Specific IgM Ab Specific neutralizing Ab, PCR</td>
</tr>
<tr>
<td><strong>Yellow Fever</strong></td>
<td>1 disseminated disease</td>
<td>Late 3rd trimester</td>
<td>Specific IgM antibody</td>
</tr>
<tr>
<td><strong>Japanese Encephalitis</strong></td>
<td>1 disseminated disease</td>
<td>Early 2nd trimester</td>
<td>Specific IgM Ab Viral isolation</td>
</tr>
</tbody>
</table>
The Incidence of Microcephaly Causally Related to Non-Zika Flavi- and Arboviruses Seems to be Very Low

This may be due to pathogen specific differences in:

1. Depression of maternal CMI or innate immune function
2. Effects on maternal-fetal placental barriers
3. Tissue tropism
4. Up regulation of inflammatory responses
Vaccines are GOOD
Disease is BAD