TORCH Infections

Krishna Dummula, MD
Case of Interest

- Baby girl E. - 24 wk GA
- 25 yr old G3 P0020 mother
- Mother presented in PTL - Born via SVD
- APGAR scores—2¹, 6⁵, and 7¹⁰; BW-584 gm, microcephaly
- Prenatal labs – none abnormal
- Hospital course notable for
  - Respiratory distress syndrome
  - Clinical Sepsis
  - PDA, s/p ligation
  - Anemia and persistent thrombocytopenia
  - NEC (DOL # 45), s/p ileostomy (DOL # 58)
  - Hyperbilirubinemia due to cholestasis
  - Germinal matrix hemorrhage
- Died at 64 days of life
  - Clinical cause of death was sepsis
- Autopsy consent was obtained – ascertain cause of death
Autopsy Findings

- **Gross findings**
  - NEC with segmental involvement of jejunum
  - Extensive peritoneal fibrous adhesions
  - Hepatic necrosis

- **Microscopic findings**
  - Intranuclear and intracytoplasmic viral inclusions characteristic of CMV
    - In kidneys, lungs, anterior pituitary gland and thyroid

- **Placental pathology**
  - Neither villitis nor inclusions were seen on H&E
  - Immunohistochemical stain for CMV – negative

- **Source of CMV infection – unclear**
  - Congenital or postnatal
  - Breast feeding / transfusion
FLAME OR BIRD?

The acronym TORCH has become common currency for a group of infections which, though heterogeneous in some attributes, share the characteristic of producing disseminated disease in the fetus and newborn. Several other infections have the same tendency but one omission from the schema is particularly disturbing, namely syphilis. I therefore propose that the letter “S” be prefixed to the acronym, giving STORCH. As the German for “stork,” the connotation with the perinatal period seems highly suitable.

I have discussed the proposal with two flawed authorities (a couple of microbiologists) and their enthusiasm for change is surpassed only by my own.

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Estimated Incidence of Perinatal TORCH Infections in U.S.

- CMV: 1% live births (5-20% of infants by 1-2 mo age)
- HSV: 0.1 - 0.5 per 1000 births
- Syphilis: 0.1 - 0.5 per 1000
- Toxoplasma: 0.1 - 0.2 per 1000
- Rubella: Approaching Zero
Index of Suspicion

When do you think of TORCH infections?

- IUGR infants
- Hepato-splenomegaly
- Thrombocytopenia
- Unusual rash
- Concerning maternal history
- “Classic” findings of any specific infection
Distinctive Features

- Intracranial calcifications (Toxo, CMV)
- Cataracts (Rubella, HSV)
- Chorioretinitis (Toxo, CMV)
- Bone lesions (Syphilis, Rubella)
- Congenital heart disease (Rubella)
- Microcephaly (CMV) ↔ Hydrocephalus (Toxo)
- Vesicles (HSV, VZV, Syphilis)
Screening for TORCH Infections

- TORCH titers – not helpful
  - Tests both IgG and IgM
  - IgM can be present for prolonged periods
    (3 months to more than an year in toxo ¹)

- Pattern of TORCH test use has a poor diagnostic return ²
  - Follow-up titers infrequently done

References:

Cost Effectiveness of Screening - Questioned

- Khan et al., 2000:
  - Examined cost and number of diagnoses of TORCH infections in 75 infants with IUGR
  - Screened with TORCH titers, urine cx., HUS
  - 3 infants had a probable infection
    - One infant by + CMV Cx.
    - Two infants by HUS
    - None had a + IgM for TORCH
  - Combined cost of evaluation = $51,715
  - Concluded – work up for TORCH infections in IUGR was not cost effective

Diagnosing TORCH Infection

- Do not use TORCH titers
- Good maternal/prenatal history
  - most infections - are mild illnesses often unrecognized
- Thorough exam of infant
- Directed labs/studies based on most likely diagnosis
## Diagnosis of TORCH Infections

<table>
<thead>
<tr>
<th></th>
<th>Serology</th>
<th>Culture</th>
<th>Histopath</th>
<th>PCR</th>
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<tbody>
<tr>
<td>CMV</td>
<td>-</td>
<td>++++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>HSV</td>
<td>-</td>
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<td>Toxo</td>
<td>++++</td>
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<td>Rubella</td>
<td>+/-</td>
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<td>Syphilis</td>
<td>+++</td>
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Cytomegalovirus
Epidemiology of Congenital CMV

- Overall birth prevalence of congenital CMV was 0.64% \(^1\)
  - 10,000 to 80,000 infants born/year with congenital CMV infection
  - Estimated annual societal cost approaches $2 billion (1991) \(^2\)
- About 11% of live-born infants - symptomatic
  - Mortality rate – 30%
  - Severe neurologic morbidity – 80%
- Transmission Rates:
  - Primary infection in mother – 32%
  - Recurrent infection during pregnancy - 1.4%
- Risk factors for congenital CMV infection
  - non-white race
  - low socioeconomic status
  - premature birth
  - NICU admittance

Natal and Postnatal Infection

Intrapartum – From Cervical and Vaginal Secretions
- 2% to 28% of seropositive pregnant women shed CMV
- Approximately 50% of exposed infants become infected
- Develop clinical signs of CMV disease at about 4 to 6 weeks of age.

Postpartum period – Breast Feeding
- 9% to 88% of seropositive women shed CMV into their milk.
- 50% to 60% of infants become infected.
- Show no significant clinical signs (re-activation disease)

Blood Transfusions
- 2-20% from unscreened or unfiltered blood

Stehel EK and Sanchez PJ. Cytomegalovirus Infection in the Fetus and Neonate. NeoReviews 2005;6:e38-e45
The Asymptomatic Congenital CMV

- 90% of congenital CMV – asymptomatic at birth
- 0.5 – 15% of these are at risk for psychomotor, hearing, neurologic, ocular, or dental abnormalities within first few years of life
- 5-10% of cases may have sensorineural hearing loss
Clinical findings - Congenital CMV

<table>
<thead>
<tr>
<th>System</th>
<th>Feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Petechiae</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Purpura, ecchymoses</td>
<td>10</td>
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<tr>
<td></td>
<td>Jaundice</td>
<td>67</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Direct bilirubin &gt; 2 mg/dL (34.2 mcmol/L)</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Elevated ALT (&gt;80 IU/mL)</td>
<td>80</td>
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<tr>
<td></td>
<td>Hepatomegaly</td>
<td>60</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>Thrombocytopenia (&lt;100 × 10³/mcL</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>(&lt;100 × 10⁹/L)</td>
<td></td>
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<tr>
<td></td>
<td>Anemia</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
<td>60</td>
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<tr>
<td>CNS</td>
<td>Microcephaly</td>
<td>53</td>
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<tr>
<td></td>
<td>Intracranial calcifications (computed tomography)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Poor feeding, lethargy</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Increased CSF protein (&gt;120 mg/dL)</td>
<td>47</td>
</tr>
<tr>
<td>Auditory</td>
<td>Sensorineural hearing loss</td>
<td>50</td>
</tr>
<tr>
<td>Visual</td>
<td>Chorioretinitis</td>
<td>10</td>
</tr>
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</table>
Diagnosing Congenital CMV

- Should be diagnosed within the first 3 weeks after birth \(^1\)
- > 3 weeks: cannot exclude the possibility of postnatal infection due to exposure to CMV in the maternal cervical-vaginal tract
- Distinction is important - because prenatal infection has been associated with long-term sequelae such as hearing impairment.
- Gold standard
  - Detection of the virus in the urine (or saliva) by cytopathic effect in tissue culture
  - Takes up to 3 weeks for results
- The shell-vial method
  - which detects early antigen production after viral infection of fibroblasts
  - can yield results in 24 hours
  - highly sensitive and specific

PCR in the diagnosis of CMV

- Preferred method for detection in CSF and amniotic fluid
- (+) CSF CMV-PCR - associated with a more severe neurologic outcome.
- (+) blood CMV-PCR - associated with development of hearing loss in infants who have congenital CMV infection.
- CMV PCR also has been performed on dried blood spot samples obtained by heel stick from newborns.
  - may offer an opportunity for screening all newborns for congenital CMV infection

1. Stehel EK and Sanchez PJ. Cytomegalovirus Infection in the Fetus and Neonate. NeoReviews 2005;6;e38-e45
2. Vauloup-Fellous C et al., Evaluation of Cytomegalovirus (CMV) DNA Quantification in Dried Blood Spots: Retrospective Study of CMV Congenital Infection. Journal of Clinical Microbiology, November 2007; 45 (11); 3804-3806
Majority of infectious chorionic villitis is due to CMV

Characteristic placental pathology

- Lymphoplasmacytic
- Stromal hemosiderin deposition
- Sclerosis and dystrophic mineralizations ("tombstones" of infected cells and villous damage)
- Intranuclear or cytoplasmic trophoblastic epithelial inclusions

Congenital CMV – Leading cause of non-genetic sensorineural hearing loss

- 23% of all prelingual hearing deficits
- Most children manifest within the first 2 postnatal years
- The hearing loss may be fluctuating and progressive
  - Hence, a complete audiologic examination should be performed as soon as possible after the diagnosis of CMV infection
  - Followed by periodic hearing evaluations for the first few postnatal years.
- Preferred hearing tests for monitoring of evolving hearing loss:
  - Audio evoked potential testing
  - Brainstem evoked potential testing

Predictors of Hearing Loss in Children with Congenital CMV

Relationship between Urine CMV titres and hearing loss

Prevention and Screening

- Mainstay of prevention
  - avoidance of exposure
  - standard precautions – hand hygiene
  - Greater risk to the pregnant health care worker → unidentified asymptomatic infant

Routine serologic screening

- Pregnant Women
  - Not recommended - no prophylactic or therapeutic interventions are available
  - Ubiquitous nature of CMV - not excluded from caring for infants who are infected with CMV

- Infant
  - Routine screening of all newborns for CMV is not recommended
  - Newborns who do not pass their hearing screen may be screened for CMV
Treatment of Congenital CMV

- Primarily - supportive care
- **Ganciclovir**
  - Inhibits viral DNA polymerase, thereby acting as a chain terminator during elongation of newly synthesized viral DNA
  - The most common adverse effect in neonates is neutropenia, which occurs in as many as 60% of recipients

Ganciclovir therapy for infants who had congenital CMV infection involving the central nervous system - I

Kimberlin, 2003: multicenter, randomized

- evaluated safety and efficacy of IV ganciclovir for 6 weeks versus no therapy
- 100 CMV-infected neonates (≥ 32 weeks of gestation, ≥ birth weight of 1,200 g)
- 47 evaluable infants – 25 ganciclovir recipients
- primary end point was improved brainstem-evoked response (BSER) between baseline and 6-month follow-up

Ganciclovir therapy for infants who had congenital CMV infection involving the central nervous system - II

- Infants from treatment group (84%) were significantly more likely to have either improved or normal hearing at 6 months than untreated infants (59%)
- At 1 or more years of age, those who received ganciclovir (0%) were significantly less likely to have worse hearing than the untreated group (41%)
- Other beneficial effects
  - significant decrease in median time to normalization of the alanine aminotransferase concentration
  - improved weight gain and head circumference after 6 weeks of therapy
  - no change in mortality
- Neurodevelopmental assessments were not performed, and it is not known if ganciclovir therapy affects the long-term prognosis in these infants

CMV – Breast Feeding

- Freezing of expressed human milk
  - 20°C for 3 to 7 days
  - significantly diminishes CMV titers
  - but does not eliminate infectivity completely
- Pasteurization (62.5°C) required for complete neutralization
  - this is not routinely done or available
- In Preterm infants
  - potential benefits far outweigh the potential risk of symptomatic CMV

Stehel EK and Sanchez PJ. Cytomegalovirus Infection in the Fetus and Neonate. NeoReviews 2005;6:e38-e45
The kinetics of CMV DNA copy numbers in breast milk

Blood Transfusions

- An important iatrogenic source
- Incidence of infection with untreated transfusates is about 15%
- Usually occurs in infants who weigh less than 1,300 g
- The risk of infection is related to:
  - volume of transfused blood
  - number of donors
  - elevated CFT titers to CMV in donor blood
Diagnosis and Screening Algorithm for CMV infection in pregnant women

Munro SC et al., Diagnosis of and Screening for CMV infection in Pregnant Women. J. Clin Micro 2005; 43 (9); 4713-4718
Toxoplasmosis
Toxoplasmosis

- Caused by protozoan – Toxoplasma gondii
- Domestic cat is the definitive host with infections via:
  - Ingestion of cysts (meats, garden products)
  - Contact with oocysts in feces
- Congenital Toxoplasmosis in the United States – 1 in 1000 to 1 in 10000
- Primary maternal infection in pregnancy → 1 in 3 risk of fetal infection
  - Infection rate higher with infection in 3rd trimester
  - Fetal death higher with infection in 1st trimester

Clinical Manifestations

- Asymptomatic at birth in 70% - 90%
- Symptoms become apparent later in life
- Classic Triad
  - Chorioretinitis *
  - Hydrocephalus
  - Intracranial calcifications
- Consequences of intrauterine meningo-encephalitis
- Initially asymptomatic infants are still at high risk of developing abnormalities, especially chorioretinitis
Diagnosis

- Maternal IgG testing indicates past infection (but when...?)
- Can be isolated in culture from placenta, umbilical cord, infant serum
- PCR testing on WBC, CSF, placenta
  - Not standardized
- Newborn
  - serology with IgM / IgA (IFA, ELISA, ISAGA)
  - IgA more sensitive than IgM

Boyer KM. Diagnostic testing for congenital toxoplasmosis. Pediatric Infect Dis J 2001; 20:59
Toxoplasma Screening

- Prenatal testing with varied sensitivity not useful for screening
- Routine neonatal screening with IgM testing implemented in some areas
  - Identifies infected asymptomatic infants who may benefit from therapy

Prevention and Treatment

- Treatment for pregnant mothers diagnosed with acute toxoplasmosis:
  - Spiramycin daily
    - Macrolide antibiotic
  - Small studies have shown this reduces likelihood of congenital transmission (up to 50%)
- If infant diagnosed prenatally, treat mom:
  - Spiramycin, pyrimethamine (anti-malarial, dihydrofolate reductase inhib), and sulfadiazine (sulfa antibiotic)
  - Leucovorin rescue with pyrimethamine
- Symptomatic infants:
  - Pyrimethamine (with leucovorin rescue) and sulfadiazine
  - Treatment for 12 months total
- Asymptomatic infants:
  - Course of same medications
  - Improved neurologic and developmental outcomes demonstrated (compared to untreated pts or those treated for only one month)

Thank You