Congenital CNS Infections

David M. Mirsky, MD
Assistant Professor of Radiology
University of Colorado School of Medicine
Director, Pediatric Neuroradiology Fellowship
Children's Hospital Colorado
Disclosures

• None
Overview

• Background

• Epidemiology

• Transmission

• Clinical Profile

• Imaging
Congenital CNS Infections

• Significant cause of perinatal mortality & child morbidity

• Risk of damage differs from infections acquired in-utero to those acquired in childhood or adulthood
  – Developing brain is very sensitive to neurotropic organisms
Congenital CNS Infections

Fetal age often more important than the type of insult

- Tissue damage is related to:
  - Pathogen specific endotoxins
  - Host’s inflammatory response

- Biological response to injury is different in fetus
  - Limited inflammatory response
  - No astroglial reaction
Congenital CNS Infections

Transmission:

- **Transplacental**
  - CMV, Toxo, Syphilis, Rubella

- **Ascension** from cervix to amniotic fluid
  - Bacteria

- **Contact** with pathogen in birth canal
  - Neonatal Herpes, Group B Strep
Congenital CNS Infections

• TORCH acronym: group of common perinatal infections with similar presentations: rash and ocular findings
  – Toxoplasmosis, Other (Syphilis), Rubella, CMV, and Herpes

• Other well-described causes of in utero infection
  – HIV, Varicella Zoster, LCMV, Parvovirus B19

• Zika virus has received much attention due to the recent outbreak in the Americas, Caribbean, and Pacific
Cytomegalovirus (CMV)

- Most common congenital viral infection
  - Prevalence of congenital CMV infection of 0.48 - 1.3%
- Symptoms: microcephaly, ventriculomeg, chorioretinitis, jaundice, HSM, thrombocytopenia, and petechiae
- “Symptomatic“ = infants with ≥ 1 symptoms at birth
  - High risk of epilepsy, delays, CP, vision loss, SNHL
  - 3000-4000 births/year
- “Asymptomatic“ = infants with no symptoms at birth
  - Some develop hearing loss or subtle symptoms later in life
CMV: Imaging

Severity of imaging findings: timing of infection

- First half of 2\textsuperscript{nd} trimester
  - Agyria/pachygyria, cerebellar hypoplasia, delayed myelination, ventriculomegaly, germinal zone cysts, perivascular calcs

- Middle of 2\textsuperscript{nd} trimester
  - Polymicrogyria, schiz, less ventriculomeg, cerebellar hypoplasia

- 3\textsuperscript{rd} trimester
  - Normal gyral patterns, mildly low volume, white matter abnormality with scattered calcifications
CMV: Imaging

• **White matter abnormalities**
  – Often affects parietal lobes, *sparing* immediate periventricular and juxtacortical white matter
  – Anterior temporal white matter *cysts/swelling*

• **Calcifications**
  – Not specific for CMV or congenital infection
    • Any injury may result in calcs (metabolic, ischemic, genetic)
  – Much more easily detected on CT than MRI
CMV: Case 1

32 wks
CMV: Case 2
CMV: Case 3
Toxoplasmosis

- 2nd most common congenital infection after CMV
- Protozoan parasite that infects animals / humans
- Infected domestic cats major source of human dz
Toxo: Clinical

• Typically asymptomatic in immunocompetent host
  – Serious disease in immunosuppressed

• Classic **triad:**
  – Chorioretinitis
  – Hydrocephalus
  – Intracranial calcifications

• Clinical (similar to CMV)
Toxo: Imaging

• Cortical destruction, white matter loss

• Ventriculomegaly/hydrocephalus (more than CMV)

• Calcifications
  – Basal ganglia, periventricular, cortex and white matter

In contrast to CMV, cortical malformations are rare!
Toxo: Case 2

DOL 1
Neonatal Herpes Simplex Virus

• Rare: 1 per 3-10,000 live births
  – Causes serious morbidity and mortality
  – 0.2% neonatal hospitalizations & 0.6% in-hospital deaths in US

• Acquired during 1 of 3 distinct time intervals
  – Intrauterine (5%)
  – Peripartum (85%): infected maternal genital tract
  – Postpartum (10%)
Both HSV-1 & HSV-2 cause the clinical disease

- **HSV-2** assoc with a poorer outcome

Low threshold for tx *(acyclovir)*

- 1-yr mortality rate disseminated dz: **29%**
- High risk of CP, epilepsy, delay in survivors
HSV: Imaging

- Intrauterine Infection
  - Calcifications
  - Ventriculomegaly
  - Encephalomalacia
  - Microcephaly

  *Appearance differs greatly from older children and adults*

- Peri- / Postnatal Encephalitis
  - Acute: Multifocal lesions affecting GW matter, temporal lobes, hemorrhage, watershed regions
    - Most apparent on DWI
  - Chronic: Diffuse, severe cystic encephalomalacia
HSV: Case 1

Neonate with irritability and respiratory distress
HSV: Case 2
Perinatal HIV Infection

• Considerable progress towards eliminating HIV in kids
  – Global burden of pediatric HIV / AIDS remains a challenge

• Transmission: pregnancy, labor, delivery, or breastfeeding

• Children most often present with diffuse encephalopathy
  – Direct effects of HIV infection
  – Immune mediators
HIV: Imaging

• Primary Infection
  – Global atrophy, ventriculomegaly
  – Basal ganglia and white matter calcifications
  – Late infection: Focal white matter lesions

• Secondary infection
  – CMV, TB, Aspergillus, Cryptococcus
  – Toxoplasmosis and PML uncommon but reported
HIV: Case 1

C/o Tamara Feygin, CHOP
Zika Virus

• Flavivirus transmitted by mosquitoes

• 1952: 1st case of Zika virus identified
  – Outbreaks since occurred in Africa, SE Asia, Pacific

• Early 2016: Global health emergency due to the outbreak in the Americas, Caribbean, and Pacific
Zika: Clinical

• Main risk is to pregnant women: 1st trimester
  – Overall risk of birth defect or abnormality: 6 – 42%

• Symptoms: low-grade fever, maculopapular pruritic rash, arthralgia, and conjunctivitis

• CDC screening for pregnant women:
  – Current/recent residence or travel to an endemic area
  – Unprotected sexual contact with the above

Zika: Pathogenesis

Neurotropic virus

• Targets and destroys neuronal progenitor cells

• Neuronal growth, proliferation, migration, and differentiation are disrupted
  – Congenital microcephaly (1-4%)

Zika: Imaging

Severity of imaging findings: timing of infection

- 1st-2nd trimester: Greatest risk of serious sequelae (55%, 52%)
  - Less likely to occur within 3rd trimester (29%)

- Most common abnormalities:
  - ventriculomegaly (33%)
  - microcephaly (24%)
  - calcifications (27%): gray-white junction

- Other:
  - atrophy, PMG, callosal dysgenesis, cerebellar hypoplasia, delayed myelination

References:
- Schuler-Faccini L. MMWR 2016.
- de Fatima Vasco Aragao M. BMJ 2016.
- Martines RB MMWR 2016.
Zika Case 1

25 weeks

C/o Dorothy Bulas, Children’s National
Zika Case 2

14 weeks

13 pts with **ABSENCE** of microcephaly at birth

- Subsequent head growth deceleration and microcephaly

**Imaging:** VMG, ↓brain volume, cortical malformations and subcortical calcifications

**Underscores the importance of neuroimaging**

Description of 13 Infants Born During October 2015–January 2016 With Congenital Zika Virus Infection Without Microcephaly at Birth — Brazil

Vanessa van der Linden, MD1; André Pessoa, MD; William Dohnyns, MD; A. James Barkovich, MD; Hélio van der Linden Júnior, MD; Epitacio Leite Rolim Filho, MD, PhD1,6; Erlane Marques Ribeiro, MD, PhD2; Mariana de Carvalho Leal, MD, PhD6; Pablo Picasso de Araújo Coimbra, MD6; Maria de Fátima Viana Vasco Aragão, MD, PhD9,10; Islane Verçosa, MD11; Camila Ventura, MD, PhD12,13; Regina Coeli Ramos, MD12; Danielle Di Cavalcanti Sousa Cruz, MD13; Marli Tenório Cordeiro, PhD14; Vivian Maria Ribeiro Mota15; Mary Dott, MD16; Christina Hillard, MA17; Cynthia A. Moore, MA, PhD17
Zika: Currently

- To date, **no** specific treatment or vaccine
  - Drug companies and NIH working towards a vaccine

- WHO: Zika no longer a global health emergency
  - Remains important pathogen with serious complication

- The full spectrum of the syndrome is still evolving
Summary

Congenital CNS infections differ from children/adults

Imaging may help with the diagnosis (specific organism)

- **CMV**: Cortical malformations, Cysts, WM lesions, Calcs
- **Toxo**: Hydrocephalus, Calcs, Lacks cortical malformations
- **HSV**: Destructive brain process: DWI
- **HIV**: Atrophy, Basal ganglia calcifications
- **Zika**: Ventriculomegaly, Microcephaly, Calcifications
Thanks!

- Dorothy Bulas: Children’s National
- Tamara Feygin: CHOP
- Jacquelyn Garcia and Mariana Meyers: Colorado
References

Questions...