Going Viral: Congenital CMV What Every Pediatrician Needs to Know

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Disclosures

I have no disclosures and no financial relationships with any ineligible companies

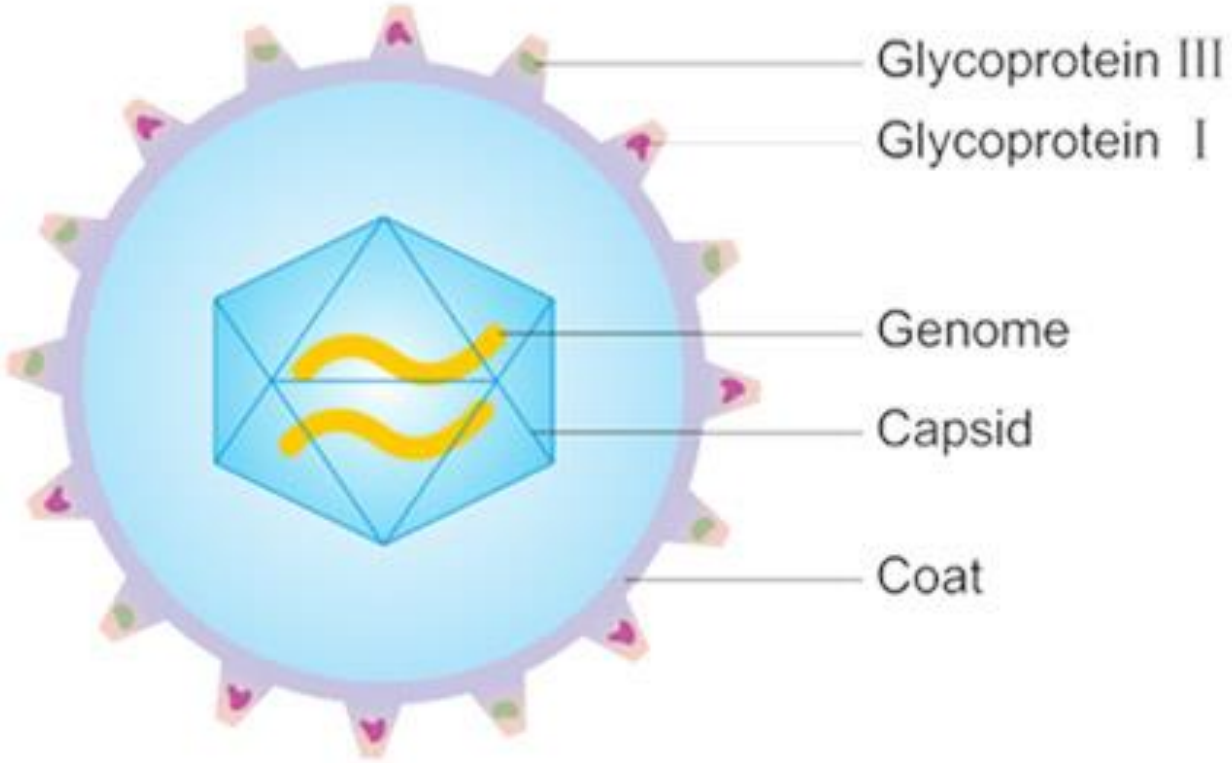
Learning Objectives

- Describe the clinical features and work-up of congenital CMV
- Know when, how to, and who needs to screen for CMV based on clinical suspicion for disease and state legislature
- Properly classify and treat congenital CMV infections as well as continue to monitor patients for possible adverse effects of therapy

What is CMV?

- Cytomegalovirus (CMV) is also known as Human herpesvirus 5 (HHV5)
- Double-stranded DNA virus belonging to Herpesviridae family

What is CMV?



What is CMV?

- Ubiquitous virus with high genetic diversity
- Spread 4 ways:
  - Horizontally – person to person through virus containing secretions
  - Vertically – From mother to infant before, during or after birth
  - Transfusion – Blood, platelets, and WBC from infected donors
  - Transplantation – Solid organ or hematopoietic cell transplantation

What is CMV?

- Once a person is infected with CMV, the virus persists in leukocytes and tissue cells indefinitely
  - Intermittent shedding occurs throughout life
  - During times of immunosuppression, symptomatic reinfection can occur
- After infection with one strain, reinfection with other strains is possible

CMV Vertical Transmission

- In utero (Congenital) – Transplacental passage of parental bloodborne virus
  - Via acquisition of a different strain during pregnancy or reactivation of an existing infection
  - Severe sequelae are associated more with infection acquired during the 1st trimester
  - Transmission rate of 32% for maternal primary infections
  - Transmission rate of <3.5% for maternal non-primary infections
  - Around half of cases of cCMV arise from each
  - Approximately 5 in 1000 infants are infected in utero and excrete CMV at birth
- At birth (Perinatal) – Passage through infected genital tract
  - Higher risk for disease if <32 weeks GA or <1500g BW
- Following birth (Postnatal) – Ingestion of CMV positive breast milk
  - Usually asymptomatic

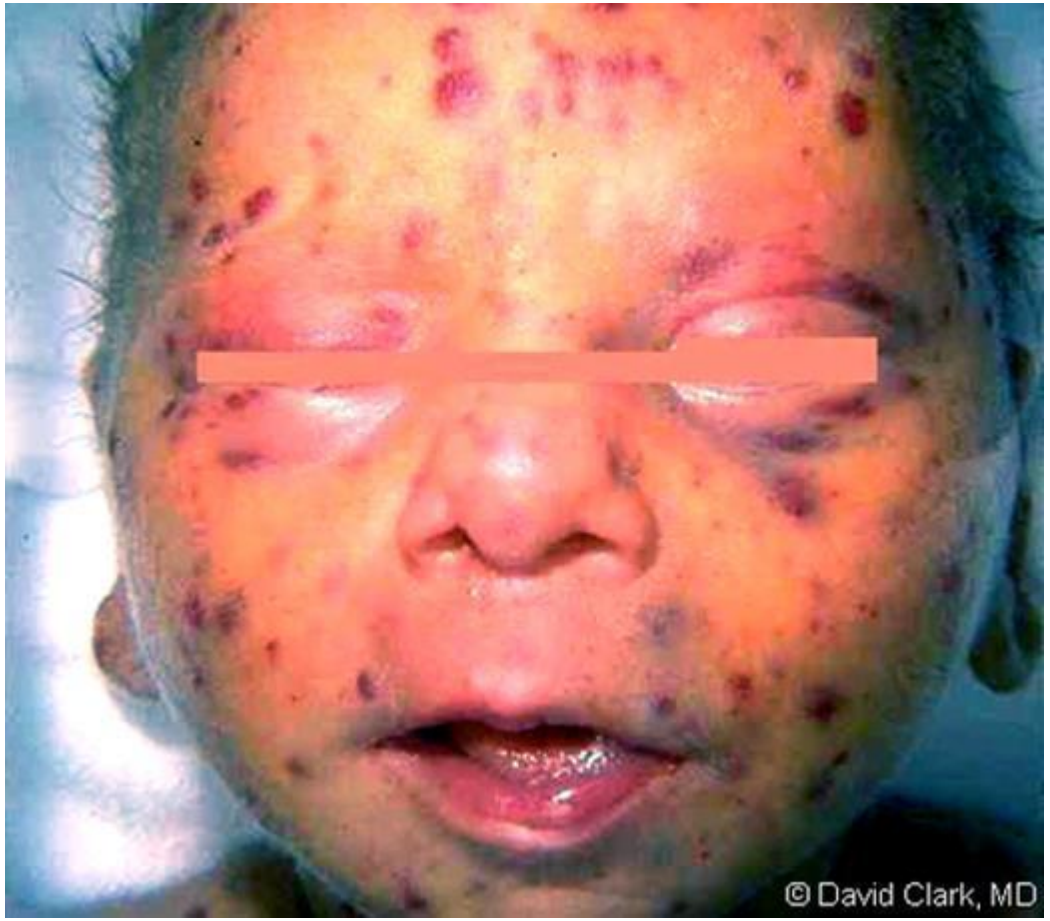
cCMV Clinical Manifestations

- 10% of infants are symptomatic at birth
  - Petechiae – 76%
  - Thrombocytopenia – 77%
  - Jaundice (direct bilirubinemia) 67%
  - Hepatosplenomegaly – 60%
  - Microcephaly – 53%
  - Retinitis – 20%
  - Purpura – 13%
  - Periventricular calcifications/Seizures – 7%
- Death in 3%-10% of symptomatic newborns
  - 0.3%-1% of all infected newborns

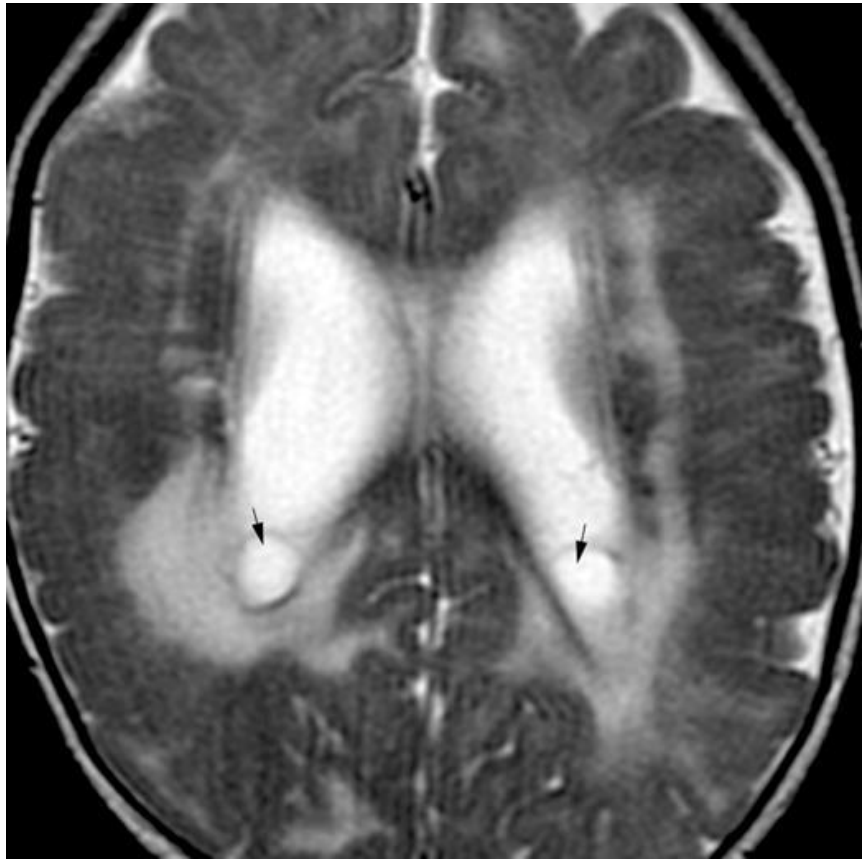
cCMV Clinical Manifestations

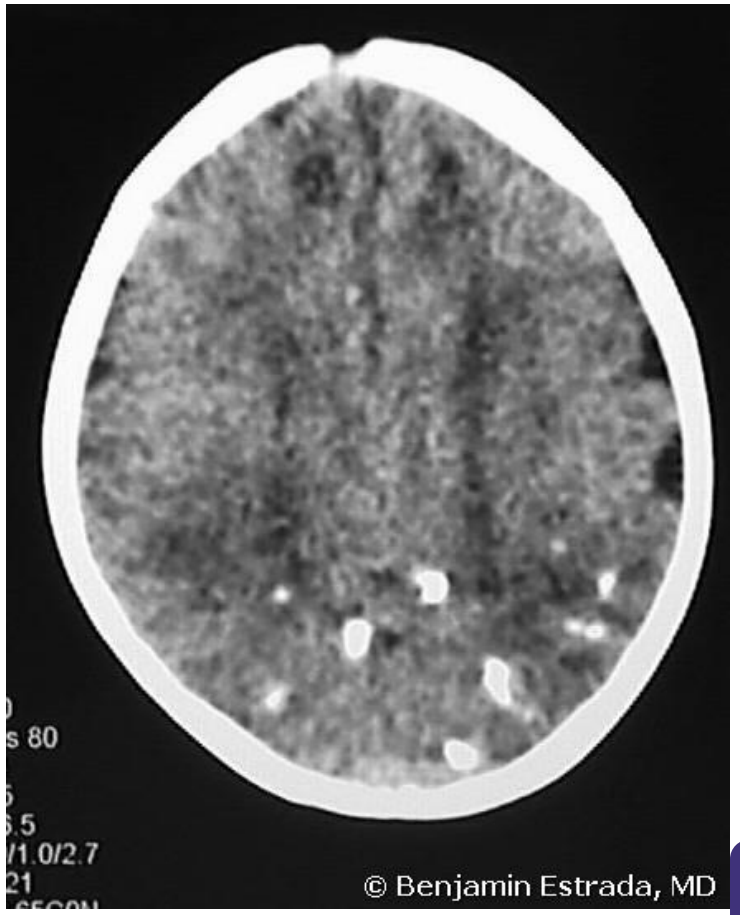
- The leading **nongenetic** cause of sensorineural hearing loss (SNHL) in the US
  - SNHL is the most common sequela following congenital CMV infection
    - Up to 50% of congenital infections that are symptomatic at birth
    - Up to 15% of asymptomatic infections
  - Continued monitoring is important!
    - ~40% of infected children who ultimately develop SNHL will not have hearing loss detectable within the first month of life
    - ~50% of children with CMV-associated SNHL continue to have further deterioration of their hearing over time

cCMV Clinical Manifestations

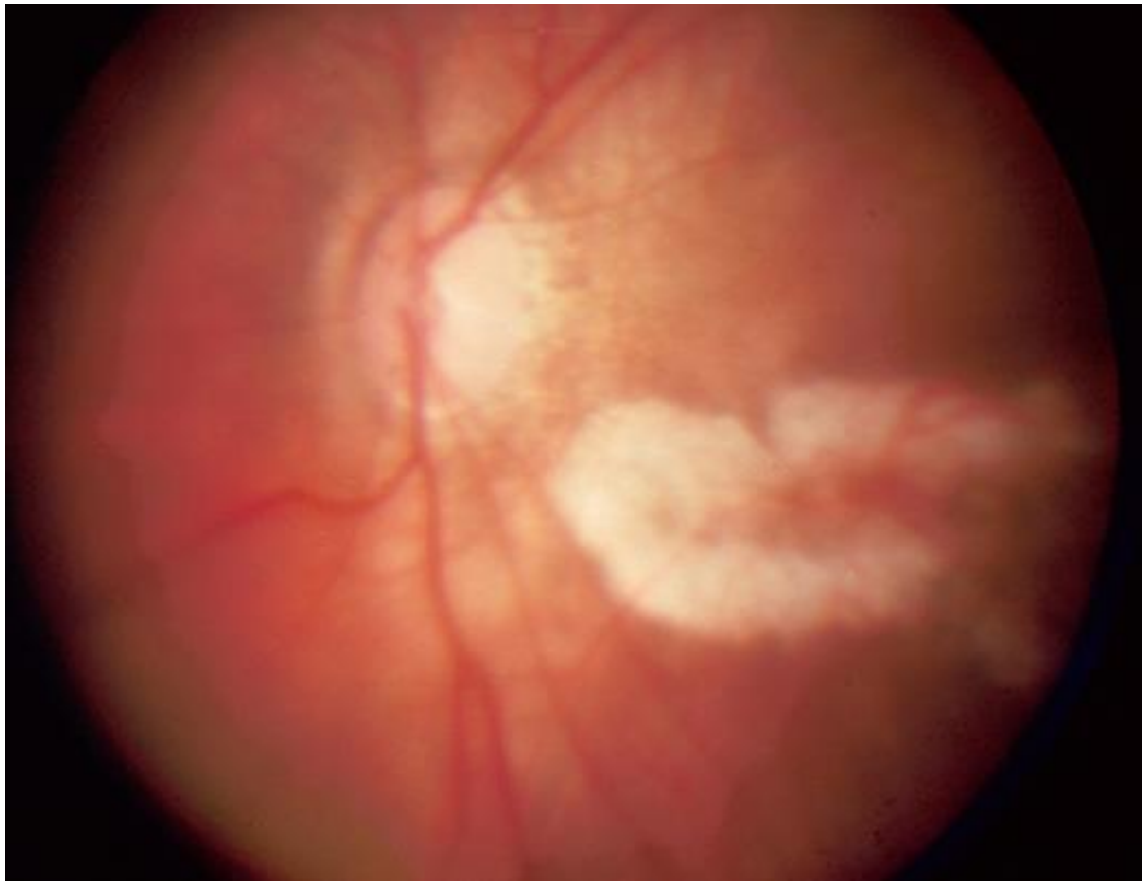


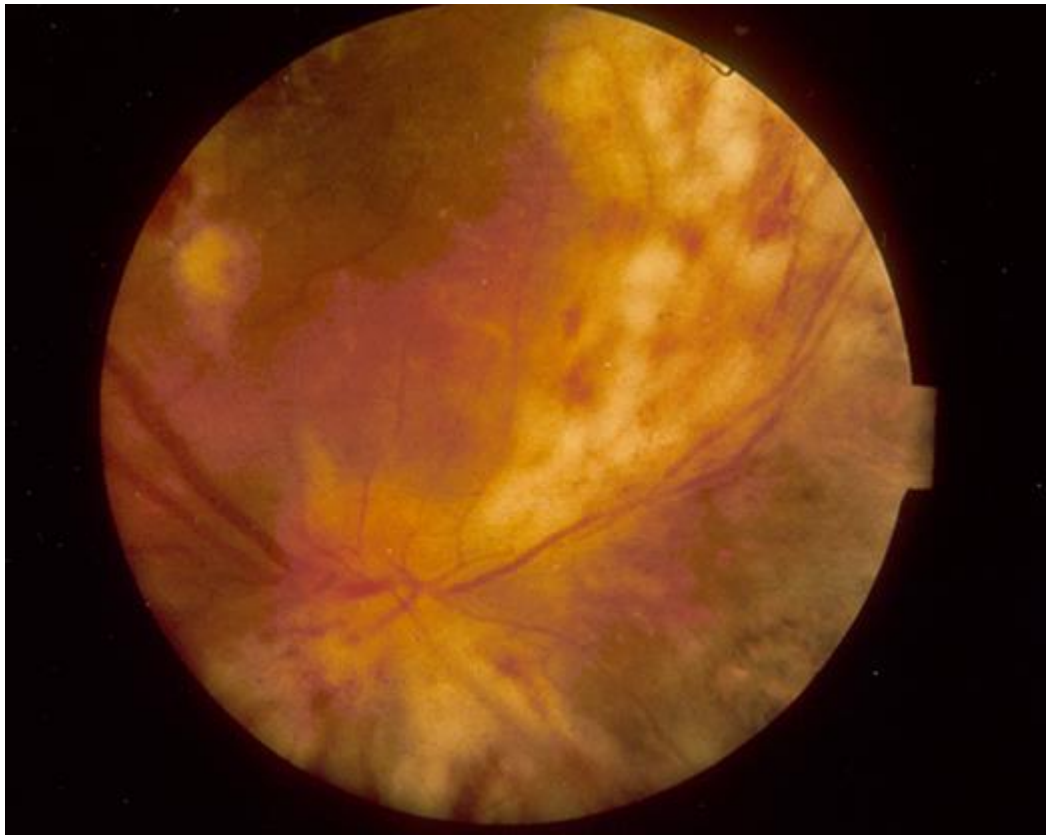
cCMV Clinical Manifestations





cCMV Clinical Manifestations





CMV Diagnostics

- Viral DNA can be detected by nucleic acid amplification tests (NAATs)
  - Tissue samples, CSF, amniotic fluid, **breast milk**, aqueous and vitreous humor fluids, **urine**, **saliva**, respiratory secretions (BAL), and **peripheral blood**
- Conventional cell cultures also available but rarely used (TAT up to 28 days)
- Serologic assays for CMV IgG and IgM available
  - IgG positivity good for screening for past infection
  - IgM positivity may be indicative of more recent infection
    - Especially when paired with a low avidity IgG

cCMV Diagnostics

- Fetal infection can be diagnosed by detection of CMV DNA in amniotic fluid
- Congenital infection requires detection of CMV or CMV DNA in **urine**, **saliva**, **blood**, or **CSF** obtained within **3 weeks** of birth
  - Note that saliva detection needs to be confirmed with urine positivity to rule-out possibility contamination with CMV positive breastmilk if breastfeeding
- Why not add it to the standard state Newborn screen?
  - The analytical sensitivity of CMV NAAT of dried blood spots is low
- IgM serology has reduced sensitivity and specificity
  - May yield false-positive results

cCMV Diagnostics

- Starting in 2019 and 2022 respectively, universal screening of all newborn infants is underway in Ontario and Saskatchewan, Canada
- In 2022, Minnesota became the first state to add congenital CMV to its newborn screening program
- Many states, including Florida, are implementing/have implemented new legislature for mandatory CMV screening in certain scenarios

cCMV Severity

- Given the wide range of clinical manifestations, cases are categorized into different tiers of severity that aid in identifying the appropriate treatment

cCMV Severity

- Asymptomatic
  - No apparent signs to suggest cCMV disease
  - Normal Hearing
  - Therapy is not recommended
- Mildly symptomatic
  - 2 or fewer transient (<2 weeks)/clinically insignificant findings
    - e.g. petechiae, thrombocytopenia, mild hepatomegaly, transaminitis
  - Insufficient date to recommend treatment at this time
  - Some treatment may be warranted on a case by case basis

cCMV Severity

- Asymptomatic with isolated SNHL
  - No clinically apparent signs to suggest congenital CMV disease
  - Sensorineural hearing loss present (failed hearing screen)
  - May offer 6 weeks of oral therapy

cCMV Severity

- Moderately to severely symptomatic, needs 1 or more of:
  - Single severe or multiorgan disease or life threatening dysfunction
  - Multiple persistent (>2 weeks) of signs attributable to cCMV:
    - Thrombocytopenia, petechiae, hepatomegaly, splenomegaly, hepatitis
  - Central nervous system involvement
    - Microcephaly, radiographic abnormalities (ventriculomegaly, intracerebral calcifications, white matter changes, periventricular echogenicity, cortical or cerebellar malformations, migration abnormalities), abnormal CSF indices, chorioretinitis, CSF CMV NAAT positivity
  - Greater than 2 mild disease manifestations
  - Treatment recommended with oral medication for **6 months**

cCMV Treatment

- Neonates with moderately to severely symptomatic cCMV disease with or without CNS involvement have improved **audiologic** and **neurodevelopmental** outcomes at 2 years of age when treated with **oral valganciclovir** for **6 months**
- Neonates with **isolated SNHL** have improved audiologic outcomes when treated with **oral valganciclovir** for **6 weeks**
- Valganciclovir is the oral prodrug of ganciclovir
  - Ganciclovir can be used to initiate therapy if GI tract is unable to absorb reliably
- Treatment should be started within first 13 weeks of life
- The dose should be adjusted each month to account for weight gain

cCMV Treatment

- Important to monitor CBCs with diff while on therapy
  - Neutropenia occurs in approx. 20% and 65% of infants on valganciclovir and ganciclovir respectively
  - Absolute neutrophil counts should be measured:
    - Weekly for 6 weeks
    - At 8 weeks
    - Monthly for the duration of antiviral treatment
  - If ANC is persistently below 500 cells/mm3, you have 2 options:
    - Hold treatment until counts recover above 750 cells/mm3
    - Administer GCSF once daily for 1 to 3 consecutive days
- Alanine aminotransferase (ALT) concentration should also be measured monthly during treatment

pCMV Treatment

- Preterm infant with symptomatic perinatally acquired infection (Not cCMV)
- Antiviral treatment has not been studied in this population
- Can be started on IV Ganciclovir
  - Reasonable approach is to treat for 2 weeks and assess responsiveness to therapy
  - If patient is responding to therapy, consider 1-2 more weeks of therapy symptoms have not resolved
- Oral Valganciclovir is not generally recommended in this age group given the high possibility of low GI absorption of the medication and degree of illness affecting the hepatic first pass metabolism of the drug

Congrats!
You are now experts on CMV in newborns!

Let's do some cases

Case 1

Case 2

Case 3

Current FL Legislature/Requirements

References

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