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CMV INFECTION and NEWBORN

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CONGENITAL CMV INFECTION (cCMV)

- Congenital CMV infection is the leading cause of **nonhereditary sensorineural hearing loss (SNHL)** and **long-term neurodevelopmental disabilities:**

✓cerebral palsy,

✓intellectual disability,

✓vision impairment,

✓seizures

- At birth, **90%** of infants with cCMV are **asymptomatic.**

- Only **10% have symptoms.**

EPIDEMIOLOGY

- cCMV infection is common worldwide. It occurs in **0.5-2.2 %** of all live births.
- The rate of cCMV infection (but not cCMV disease) is proportional to the seroprevalence of CMV in women of childbearing years.

✓Areas of high CMV seroprevalence (80-100 %): cCMV infection rates range from 1-5 %

✓Areas of relatively low CMV seroprevalence (40-70 %): cCMV infection rates range from 0.4-2 %

INFECTION / TRANSMISSION

- CMV has the biological properties of **latency and reactivation.**

1. **Primary maternal infection:** Most often results from close contact with young children*.
2. **Recurrent infections:** Occur through reactivation of the host's endogenous strain of CMV or reinfection with a new exogenous strain.

- The risk of **vertical transmission** to the fetus is far higher with primary maternal infection than with recurrent infection (32 vs 1.4 %)

- Transmission risk is also associated with **maternal age and parity** (*The risk is increased in younger, primigravid women)*

CLINICAL MANIFESTATIONS

- Infants are more likely to have symptoms at birth and suffer long-term sequelae in the setting of primary maternal infection.
- The risk of hearing loss appears to be similar in both primary and recurrent infections.
- Sequelae appear to be more severe when infection is acquired earlier in pregnancy, particularly in the first trimester.

CLASSIFICATION

1. **"Symptomatic cCMV Infection":** Infants with one or more symptoms at birth. It may result from maternal infection at any time during pregnancy.

2. **"Asymptomatic cCMV Infection":** Infants with no apparent symptoms at birth (some may develop hearing loss or subtle symptoms later in life)

3. **"Asymptomatic cCMV Infection with Isolated Hearing Loss":** Infants with isolated hearing loss at birth but no other symptoms.

CLINICAL MANIFESTATIONS

IN UTERO

- The fetus may be **silently infected** or manifest **CMV disease** in utero.
- Findings on prenatal ultrasound:

✓**periventricular calcifications**,

✓migrational abnormalities of the brain,

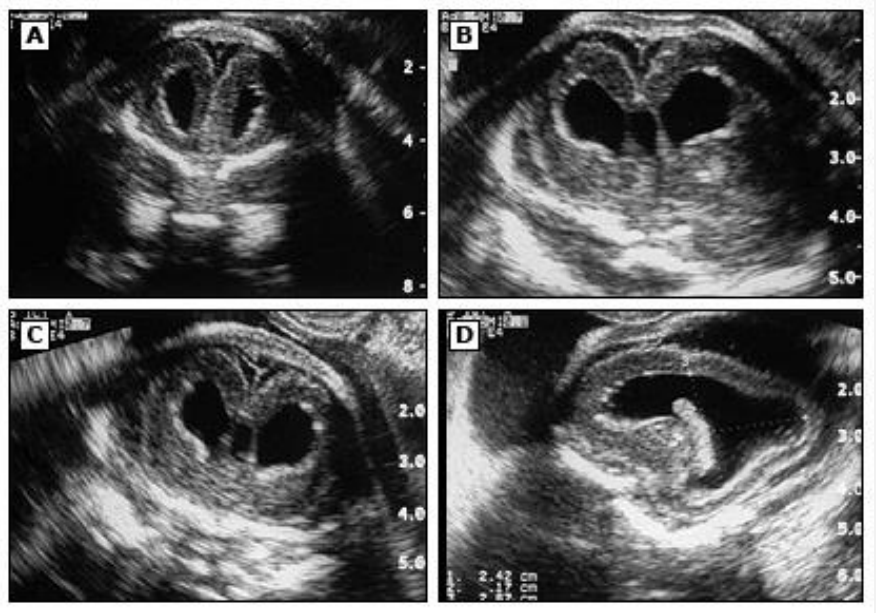
✓microcephaly,

✓hyperechogenic fetal bowel,

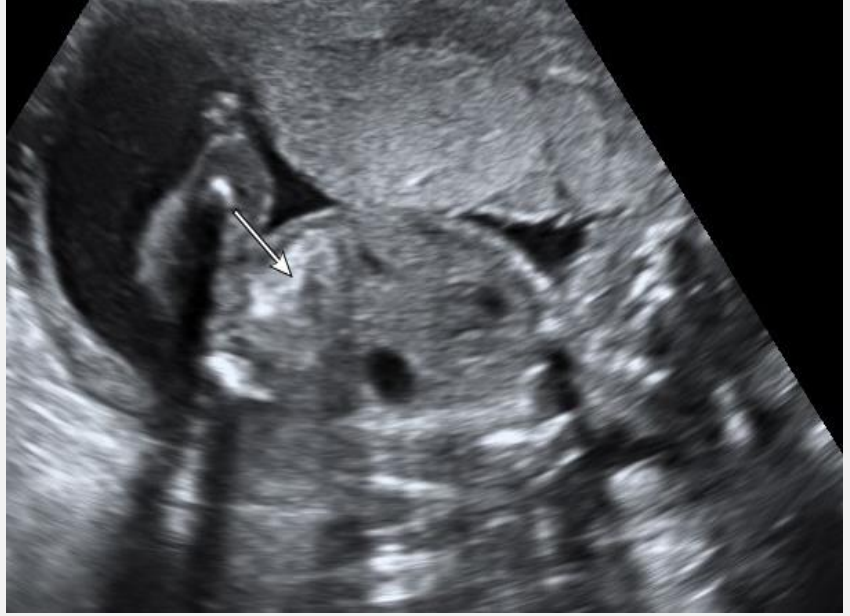
✓fetal growth restriction,

✓ascites and/or pleural effusion,

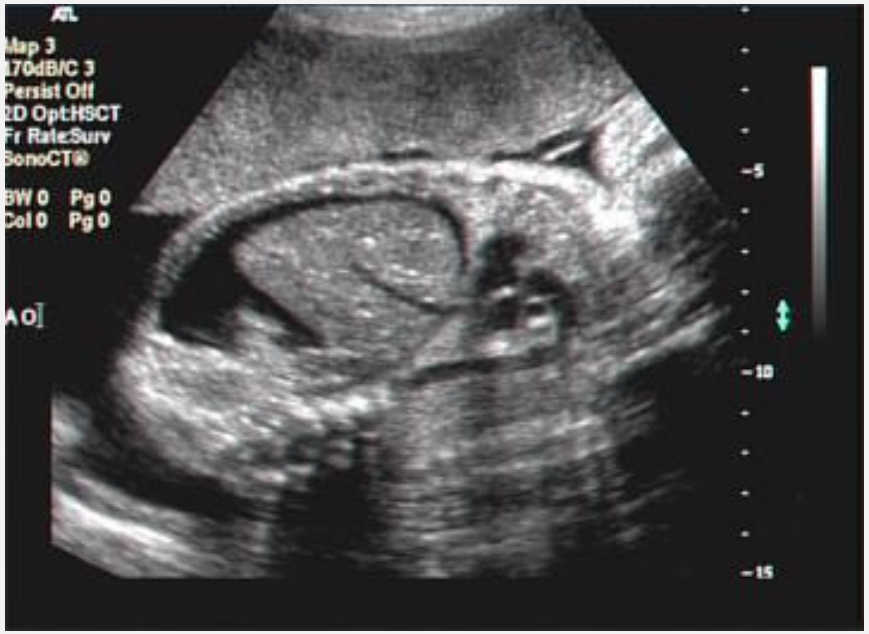
✓hepatosplenomegaly



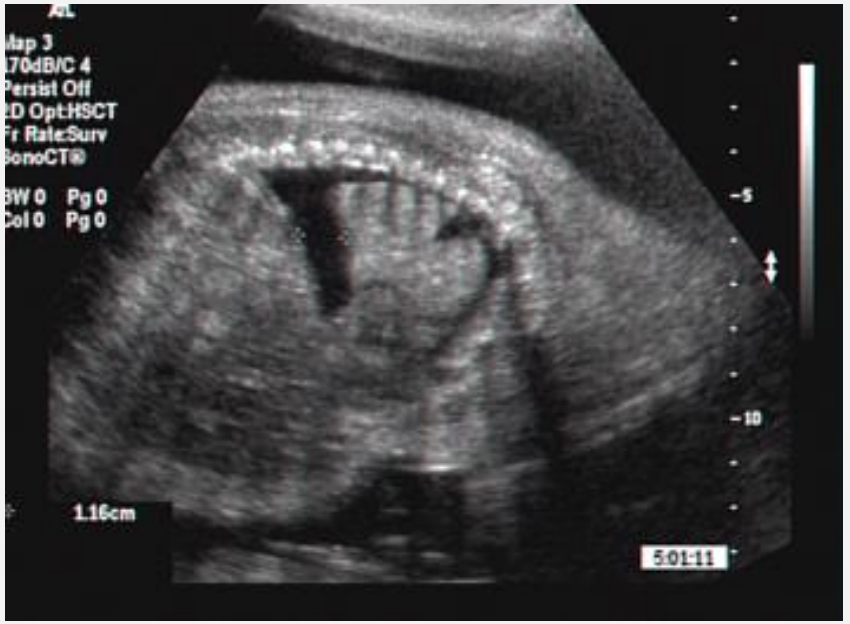
Dilation of the LVs and PV calcifications



Echogenic fetal bowel



Fetal ascites



Unilateral pleural effusion

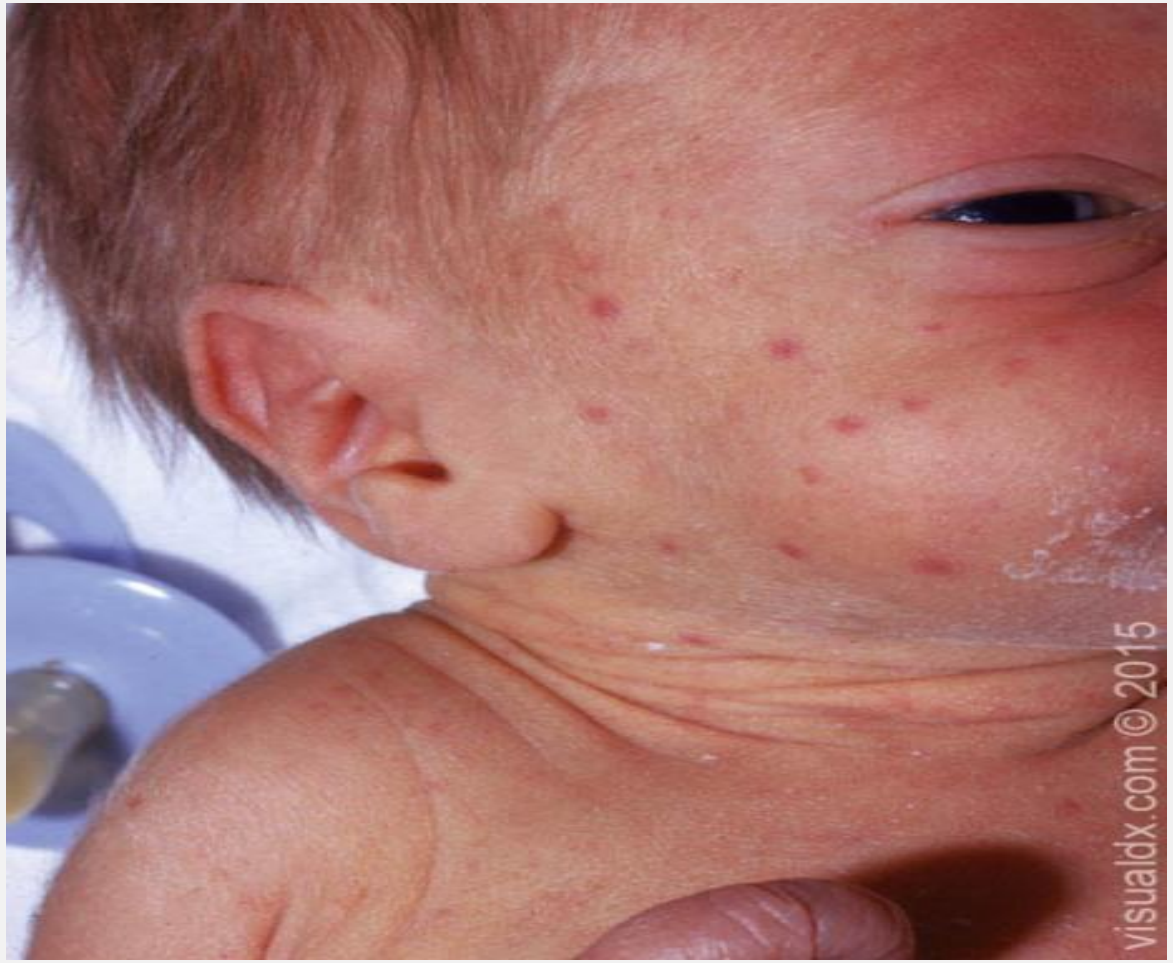
Demmler-Harrison GJ, UpToDate 2019

I. SYMPTOMATIC INFECTION

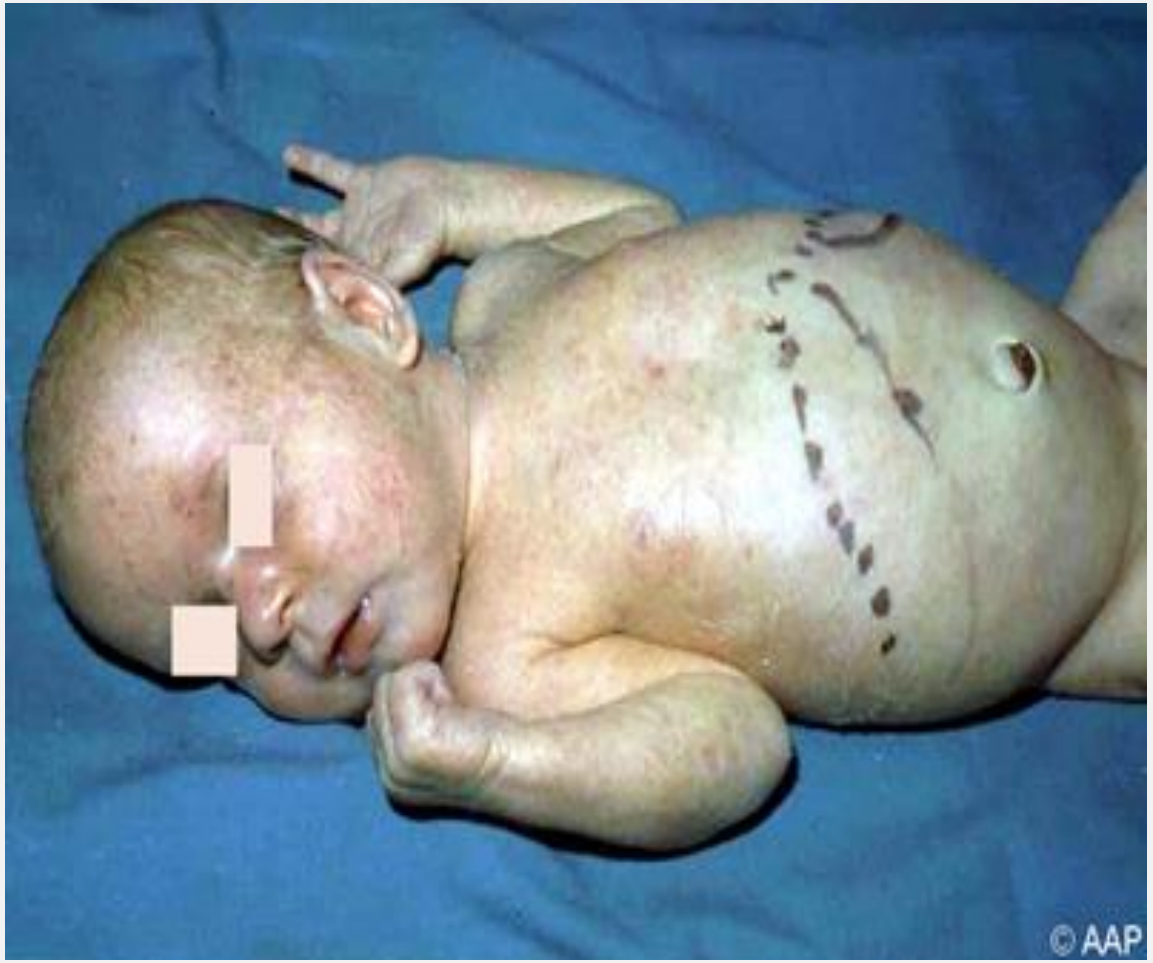
CLINICAL MANIFESTATIONS

- Petechiae (54-76 %)
- Jaundice at birth (38-67 %)
- **Hepatosplenomegaly** (39-60 %)
- Small size for gestational age (39-50 %)
- **Microcephaly** (36-53 %)
- **Sensorineural hearing loss** (present at birth in 34 %, delayed SNHL can also occur)

- Lethargy and/or hypotonia (27 %)
- Poor suck (19 %)
- Chorioretinitis (11-14 %)
- Seizures (4-11 %)
- Hemolytic anemia (11 %)
- Pneumonia (8 %)



Symptomatic Term Neonate Jaundice, diffuse petechiae and purpura

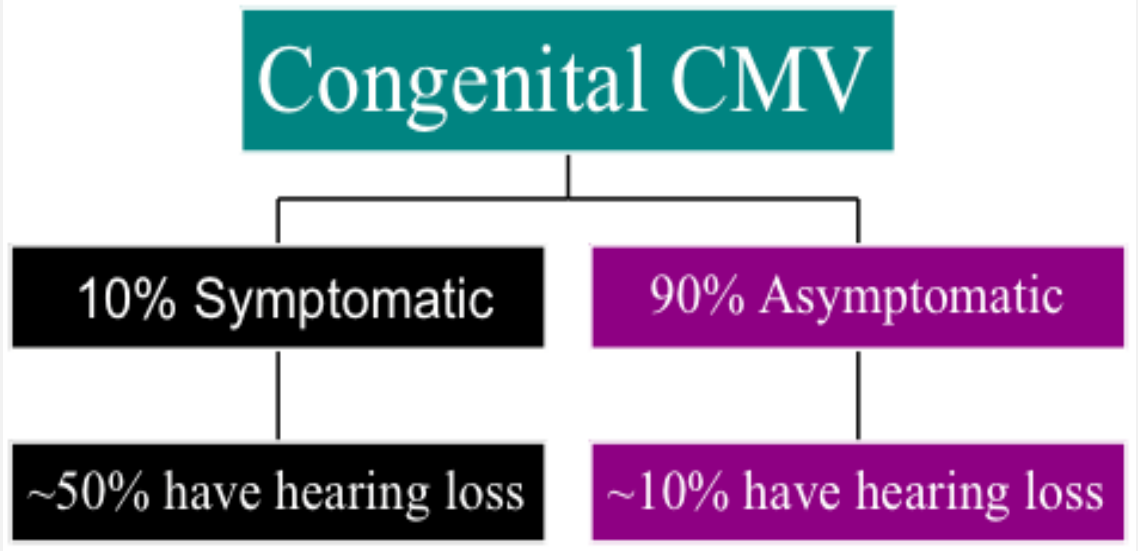


Blueberry muffin rash, petechiae, HSM, anemia

Demmler-Harrison GJ, UpToDate 2019

SENSORINEURAL HEARING LOSS (SNHL) How common in cCMV?

- It's detected in **1/3-1/2** of infants with **symptomatic** disease and **1/10** of **asymptomatic** infants.
- It may be detectable at birth, but in 18-30 % of cases it has delayed onset.
- SNHL associated with symptomatic cCMV is often progressive (18-63 %) and eventually becomes severe to profound in the affected ear(s) of 78 % of children.



LESS COMMON FINDINGS

- Ascites
- Myocarditis
- Cardiomyopathy
- Ventricular trabeculations
- Enterocolitis
- Endocrinopathies (Grave's disease, DI)
- Renal disease (Nephrotic syndrome)

Some infants may only present with isolated microcephaly at birth.

LIFE-THREATENING DISEASE

- **~ 8-10 %** of newborns with symptomatic cCMV infection, especially premature infants, have severe disease.

- Many infants with fulminant disease die within days or weeks due to **viral-associated hemophagocytic syndrome or severe end-organ disease.**

- Mortality rate is **~ 30 %** *(The overall mortality rate among infants with cCMV infection: 4-8 % within the first year of life)*

- In survivors, jaundice and HSM may subside, but neurologic sequelae persist.

PREMATURE INFANTS

- 25-35 % of infants with symptomatic cCMV are born at <37 w
- When compared to term neonates premature neonates <32 w with symptomatic cCMV are;
- **MORE LIKELY TO HAVE**

✓pneumonia,

✓signs of viral sepsis,

✓thrombocytopenia,

✓co-infections

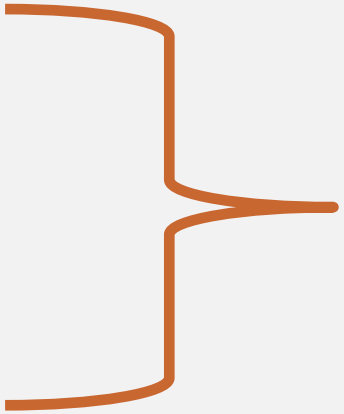
- **LESS LIKELY TO HAVE**

✓microcephaly

✓intracranial calcifications

LABORATORY FINDINGS

- Elevated liver transaminases (50-83 %)
- **Thrombocytopenia** (48-77 %)
- Elevated direct and indirect serum bilirubin (36-69 %)
- Hemolytic anemia
- Neutropenia
- Lymphopenia/ lymphocytosis



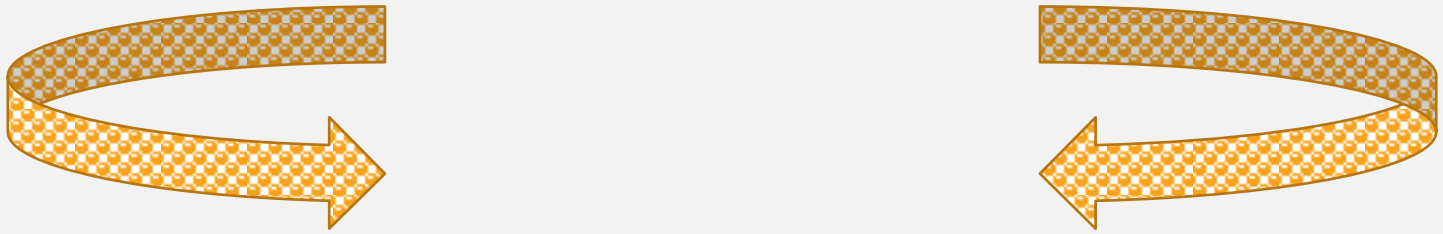
less common findings

- Elevated CSF protein level

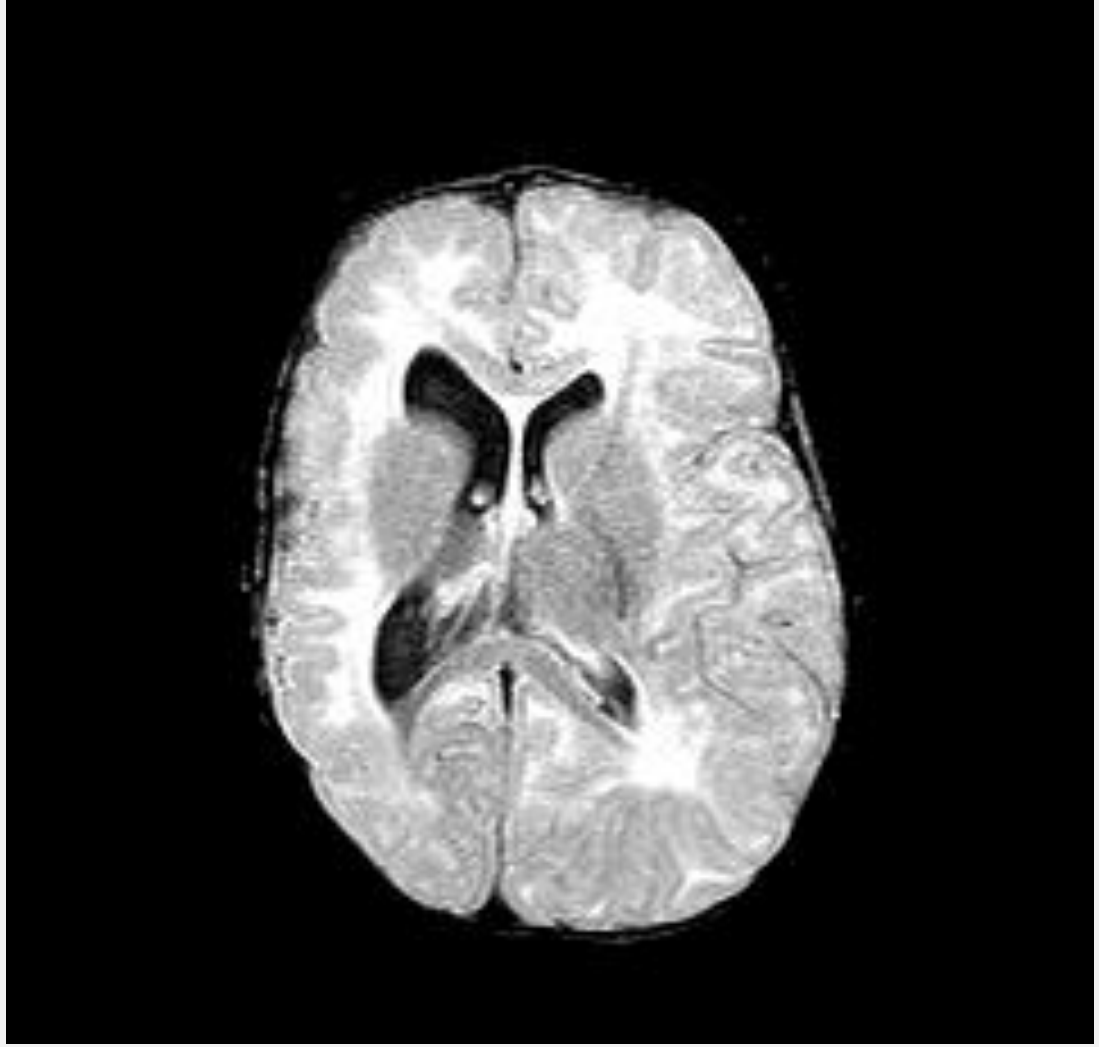
NEUROIMAGING

- ✓**Intracranial calcifications,** usually periventricular (34-70 %)
- ✓Lenticulostriate vasculopathy (27-68 %)
- ✓White matter disease (22-57 %)
- ✓Ventriculomegaly (10-53 %)
- ✓Migrational abnormalities (focal polymicrogyria, pachygyria, lissencephaly) (10-38 %)
- ✓Periventricular leukomalacia and cystic abnormalities (11 %)

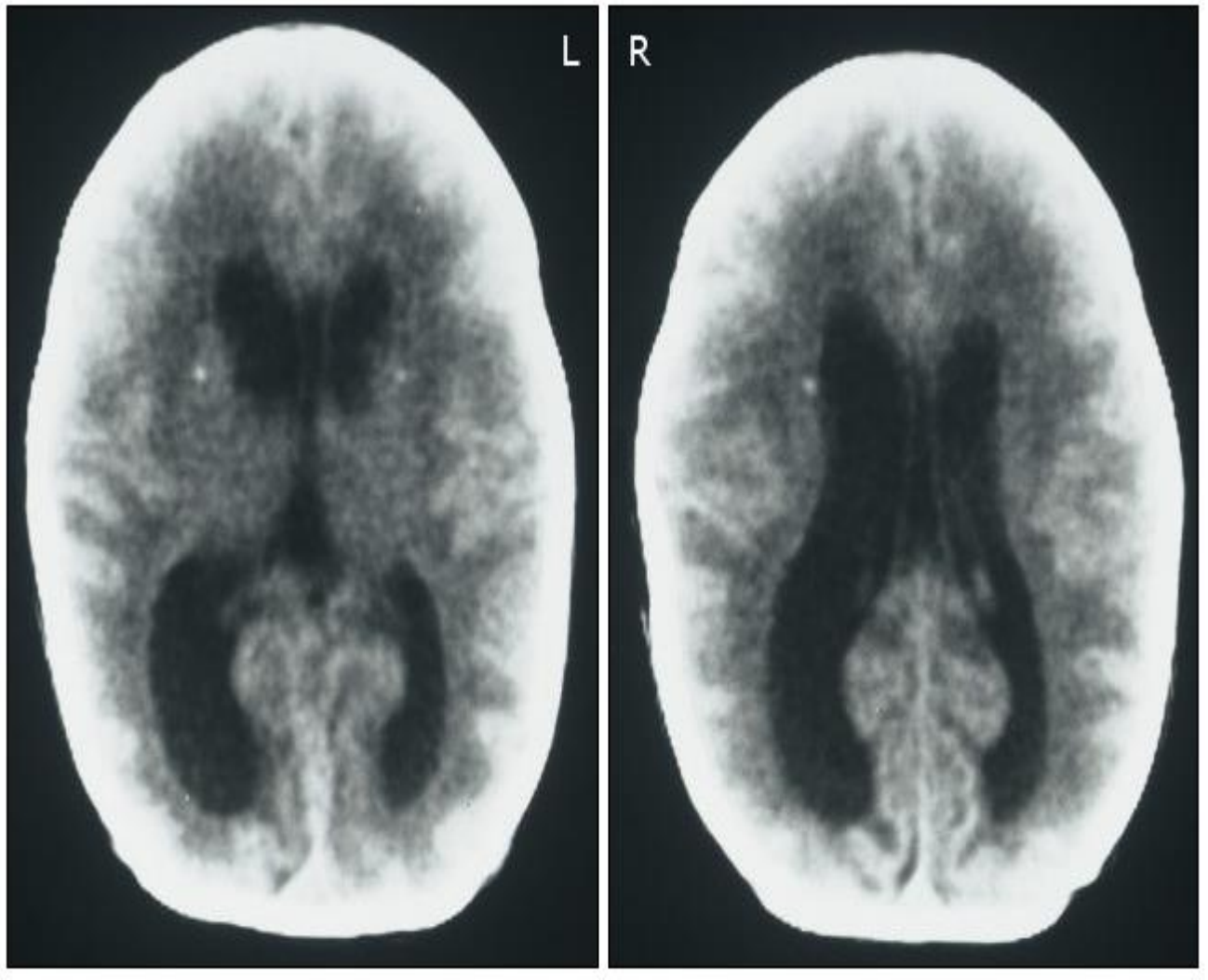
MICROCEPHALY+ INTRACRANIAL CALCIFICATIONS



POOR LONG-TERM NEURODEVELOPMENTAL OUTCOME



Brain MRI: Unilateral cortical maldevelopment and polymicrogyria



CCT: Bilateral ventriculomegaly, punctate PV calcifications

Demmler-Harrison GJ, UpToDate 2019

II. ASYMPTOMATIC INFECTION

- **90** % of newborns with cCMV infection are apparently **asymptomatic at birth.**
- Nonetheless, subtle differences may be peresent (LBW, slightly earlier gestational age)
- **10-15** % of otherwise asymptomatic newborns experience **SNHL.**
- 1-2 % develop ocular abnormalities (retinal lesions, strabismus) (rarely sight-threatening)
- 5-20 % may have abnormal brain imaging findings.

ASYMPTOMATIC WITH ISOLATED HEARING LOSS

- **10-15** % of apparently asymptomatic newborns experience **SNHL.**
- Universal newborn hearing screening programs may identify some of these infants.
- In a study of 572 infants who failed newborn hearing screening;
  - ✓6% were found to have cCMV infection
  - ✓75% of infants with cCMV infection were identified solely on the basis of the newborn hearing screen.

Stehel EK et al. J AAPOS 2000.

III. ASYMPTOMATIC WITH ISOLATED HEARING LOSS

- Systematic review of 37 obsevational studies: asymptomatic vs symptomatic infants;

ASYMPTOMATIC INFANTS HAD

✓less frequently delayed onset HL (9 vs 18%)

✓less frequently bilateral severe to profound HL (43 vs 65%)

✓similar rates of progressive HL (20%)/ fluctuating HL (20-25%)

Goderis J et al. Pediatrics 2014

LATE COMPLICATIONS

- 70-80 % of infants **symptomatic at birth** develop late complications:
  - ✓**Hearing loss**
  - ✓Vision impairment
  - ✓Dental abnormalities
  - ✓Intellectual disability (varying degrees)
  - ✓Delayed psychomotor development

- **Asymptomatic cCMV** infants may develop:
  - ✓**Hearing loss** (most common)
  - ✓Neurocognitive delay (subtle, involve one area of learning)
  - ✓Language delay

DIAGNOSTIC APPROACH

cCMV should be suspected in the following clinical scenarios:

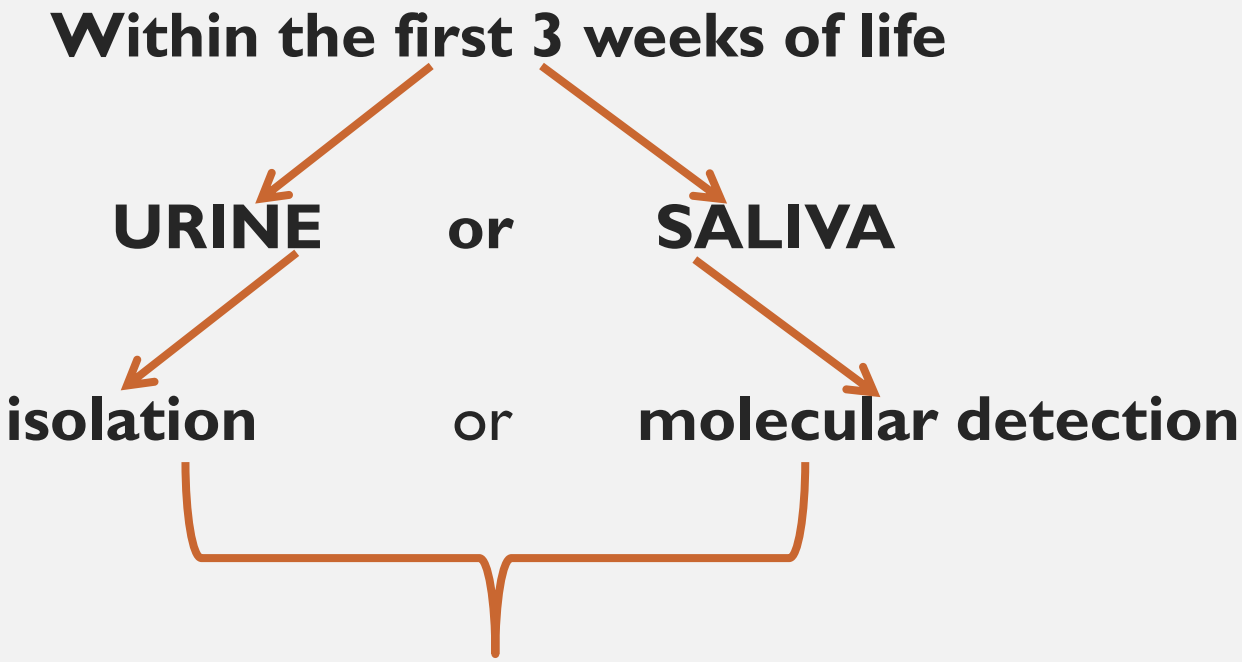
1. **Newborns with signs and symptoms consistent with cCMV disease** *(microcephaly, SGA, thrombocytopenia, HSM, jaundice)*

2. **Newborns with abnormal neuroimaging consistent with cCMV** *(if the findings aren't explained by other causes)*

3. **Newborns who have documented SNHL** *(whether or not they have other symptoms of cCMV)*

4. **Newborns born to mothers with known or suspected CMV infection during pregnancy** *(maternal seroconversion during pregnancy, maternal primary CMV infection with positive CMV IgM and IgG)*

LABORATORY TESTING



1. Viral culture
2. Modified culture (rapid culture/ shell vial assay)
3. PCR

LABORATORY TESTING

- Testing blood samples isn't recommended as a first-line test because not all infected infants are viremic.

- Detection of **CMV DNA by PCR** in blood samples can be diagnostic but serologic testing for **CMV IgM** isn't recommended since it's less sensitive and less specific.

- cCMV infection may be retrospectively diagnosed by PCR analysis of **dried blood samples** (Guthrie cards) obtained for newborn screening.

INTERPRETATION of TEST RESULTS

Virologically-proven cCMV Infection

1. Positive viral culture (urine/saliva) within the first 3 weeks

2. Positive shell vial assay (urine/saliva) within the first 3 weeks, with a positive confirmatory test (viral culture/ PCR)

3. Positive PCR (urine/saliva/blood) within the first 3 weeks, confirmed on repeat testing

4. Positive PCR in the newborn screening dried blood spot, with a positive confirmatory test (viral culture/ PCR) if the infant is <3 weeks old.*

POST-DIAGNOSIS EVALUATION

- A thorough physical, neurologic/ neurodevelopmental examination
- Laboratory tests.....CBC, liver and kidney function tests, coagulation studies
- Hearing evaluation by auditory brainstem response (ABR)
- Ophtalmology evaluation
- Neuroimaging…….USG/ CT/ MRI
- CMV DNAemia by quantitative PCR of blood for infants receiving antiviral therapy

DIFFERENTIAL DIAGNOSIS

- **Other TORCH infections** (*including Zika virüs infection)*
- **Neonatal sepsis**
- Genetic, metabolic and toxic disorders presenting with abnormal neurologic findings (*Galactosemia, UCD, organic acidemias, LSD, peroxisomal disorders, IU alcohol & cocaine exposure)*
- Disorders presenting with hepatitis and hyperbilirubinemia *(viral hepatitis, ischemic injury, thrombosis, hemolytic disease, biliary atresia, α-1-antitrypsin deficiency)*

NEWBORN SCREENING for cCMV

- Newborns aren't routinely screened for CMV. Given the substantial public health impact of cCMV, experts support **TARGETED** and/or **UNIVERSAL** newborn screening.

- The goals of newborn screening:
  - ✓Early identification of infected infants with subtle symptoms who may benefit from antiviral therapy.
  - ✓Identification of asymptomatic infants who are at risk for delayed SNHL and warrant more frequent audiologic evaluation.

GANCICLOVIR TREATMENT *(Pass RF, J Infect Dis 1999)*

Pro-

- Antiviral effect
- Might prevent death or improve newborn disease
- No other options

Con-

- Most damage done prior to birth
- Limited antiviral effect
- Potential reproductive toxicity
- Potential 'rebound' retinitis or other disease
- Lack of evidence of efficacy

GANCICLOVIR TREATMENT *(Kimberlin DW, J Pediatr 2003)*

- Multi-center, phase III, randomized, controlled trial
- 100 symptomatic neonates with CNS involvement
- 42 subjects used in analysis
- 6 weeks GCV (6mg/kg q12h) vs no treatment
- Outcome: Hearing improvement, or for those with normal hearing at baseline, preservation of normal hearing at 6 months of age

- GCV recipients had improved or protected hearing at 6 months (84% vs 59%)
- None of the GCV recipients had hearing deterioration at 6 months.
- At 1 year 21% of GCV recipients had worsening in hearing in their best ear, as compared with 68% in the non-treated group.
- Neutropenia was 3 times more common in treated infants.

GANCICLOVIR TREATMENT *(Kimberlin DW, J Pediatr 2003)*

- This study raises many questions. Because it is unknown whether

?? improvement in hearing would be maintained long-term ??

?? what the impact of improved hearing is in infants with a high risk of developmental problems ??

- Viral excretion in urine returns to pretreatment levels within 2 weeks after GCV is discontinued, as does viral load.

- Carcinogenicity and gonadotoxicity of GCV in some animal models ??

GANCICLOVIR TREATMENT CAN BE CONSIDERED FOR SYMPTOMATIC INFANTS, BUT CANNOT BE ROUTINELY RECOMMENDED !!!

PROLONGED VALGANCICLOVIR TREATMENT *(Kimberlin DW, NEJM 2015)*

- Phase III, randomized, placebo-controlled trial
- 96 symptomatic infants with or without CNS involvement
- 86 subjects used in analysis
- 6 weeks oral VGCV vs 6 months oral VGCV
- Primary end point: Change in hearing in the better ear from baseline to 6 months *("best-ear" hearing)*
- Secondary end point: Change in hearing from baseline to follow-up at 12 and 24 months and neurodevelopmental outcomes,

- Best-ear hearing at 6 months was similar.
- Total-ear hearing was more likely to be improved or to remain normal at 12 months in the 6-month group (73% vs 57%)
- The benefit in total-ear hearing was maintained at 24 months (77% vs. 64%)
- At 24 months, the 6-month group had better neurodevelopmental scores on the Bayley Scales

PROLONGED VALGANCICLOVIR TREATMENT (*Kimberlin DW, NEJM 2015*)

- Based on this study;

  VGCV for 6 months is now considered an effective and well-tolerated therapeutic option for symptomatic infants to improve hearing and neurodevelopmental long-term outcomes !!!

- **However there is still no evidence of benefit of antiviral therapy in asymptomatic infants.**

THE DECISION TO START ANTIVIRAL THERAPY IN INFANTS WITH SYMPTOMATIC cCMV INFECTION SHOULD INVOLVE ADEQUATE COUNSEL REGARDING THE POTENTIAL BENEFITS AND RISKS OF THERAPY.

PREVENTION

- Women childcare workers, women health care workers should be counseled.
- Good hygiene, including hand washing and not kissing on the mouth, should be taught to all pregnant women.
- Vaccines are being studied ??
- Passive immunization with CMV-specific hyperimmune globulin during primary/ recurrent maternal infection ??

Thank you .....