# Congenital CMV in the COVID Era: Overview of Pre and Post-natal CMV Imaging and Our Experience with CMV COVID-19 Co-infection

Beaumont

Ryan Kelsch, DO[1]; Carol Lima, MD[1]; Anant Krishnan, MD[1]

Department of Diagnostic Radiology and Molecular Imaging ▪ Beaumont Hospital, Royal Oak, MI

OU WB School of MEDICINE

## Objectives

1. To present the expected pre and postnatal imaging findings of CMV infection through recent case examples from our institution and indicate some of the critical findings that may lead to their appropriate detection and confirmation.
2. To present examples of congenital CMV in mothers with proven COVID-19 co-infection
3. To discuss possible implications of CMV COVID-19 co-infection

**KEY:** MR=Magnetic Resonance; CMV=Cytolomegalovirus; COVID-19=Coronavirus Disease 2019

## Introduction

CMV infection is the most common fetal infection. There is much known about the imaging manifestations of pre and postnatal CMV infection. While there is growing recognition of SARS-CoV-2 infection in mothers, there still much unknown about the manifestation in the fetus and its relationship to other in-utero infections.

## Prenatal CMV Imaging

Prenatal brain imaging findings with maternal CMV infection include:

- White matter hyperintensities on T2 weighted imaging especially **temporal pole hyperintensities and cysts**
- Ventriculomegaly
- Periventricular and intraventricular **septations and cysts**
- **Cortical malformations** including polymicrogyria
- Periventricular **calcifications** (seen as punctate low T2 signal/high T1 signal, can be in other areas)
- Microcephaly
- Findings that can be seen outside the brain which can hint at CMV include **hepatosplenomegaly, hydrops fetalis**, echogenic bowel and micropthalmia.

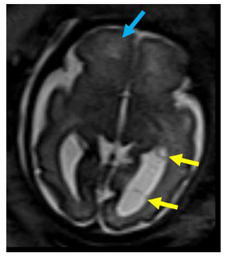

*Figure 1. Prenatal fetal MR axial T2 HASTE image at 32 weeks gestation demonstrates parenchymal T2 hyper… tensities (blue arrow) and dilated lateral ventricles with intaventricular cysts (yellow arrows)*

The imaging findings of CMV are dependent on the timing of infection during gestation. For example, early infection (<18 weeks) tends to more severely affect the fetus, with more profound microcephaly, ventriculomegaly, brain volume loss, and periventricular calcifications. Migration abnormalities also tend to me more common the earlier the infection is in the pregnancy.

Some of these findings can be seen on fetal ultrasound, but **MR is helpful in identifying cortical malformations**, and greatly improves **confidence in the diagnosis**. In our institution, in a few cases the condition had not been suspected by US (the common indication for MRI was ventriculomegaly) and it was the MR suspicion that led to maternal testing for CMV antibodies and postnatal fetal urine confirmation. Figure 1 shows an example of some of these findings.

## Postnatal CMV Imaging

The immediate postnatal imaging findings of CMV infection in the neonate are similar to those seen in-utero. The findings are often more obvious due to the increased spatial and contrast resolution that post-natal imaging affords. A few additional things to keep in mind on postnatal imaging include:

- CT can be used to help confirm calcifications (alternatively SWI on MRI)
- Delayed myelination may be detected
- Lentriculostrate vasculopathy/Mineralizing vasculopathy can be see on ultrasound as hyperechoic streaks in the basal ganglia, although this finding is non-specific. Figure 2 shows some examples of these findings.

## CMV in the COVID-19 Era

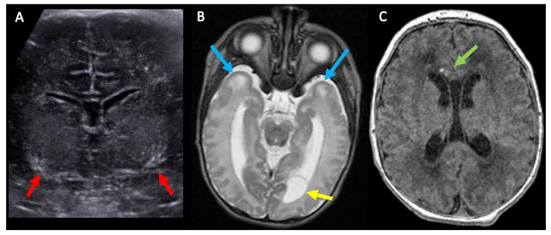


*Figure 2. A: Postnatal coronal head US from the same patient in figure 1 at 2 days age demonstrates mineralizing lenticulostriate vasculopathy (red arrows). B, C: postnatal MR axial T2 and gradient T1 images at 2 weeks old demonstrate similar parenchymal hyperintensities in the temporal poles (blue arrows) and dilated lateral ventricles cysts (yellow arrow), and presumed periventricular calcifications (green arrow).*

Our institution's database of fetal imaging was queried for mention of CMV infection on fetal MR imaging. Cases which included only ultrasound imaging were excluded given limitations in brain assessment. After the beginning of the COVID-19 pandemic in 2020, CMV infection was suggested on fetal MR reports 4 times. This seemingly was an increase in CMV prevalence compared to prior to the pandemic at our institution. These 4 cases were analyzed further, with laboratory and imaging findings summarized in table 1.

| Patient Number | Date of Exam | Maternal Age | Fetal Gestational Age (weeks) | Fetal MR Findings | Postnatal Imaging Findings | COVID-19 Maternal Test Result (PCR) | CMV Maternal Test Result (Serum IgG, IgM) | CMV Neonatal Test Result |
|---|---|---|---|---|---|---|---|---|
| 1 | 02/13/20 | 24 | 37 | Lateral ventriculomegaly, abnormal white matter signal | Head ultrasound showed ventriculomegaly, subependymal cysts, and mineralizing vasculopathy | Negative | Positive (IgM and IgG) | Positive (PCR urine) |
| 2 | 12/22/20 | 39 | 30 | Small brain volume, ventriculomegly with cystic areas, periventricular calcifications or hemorrhage | Head ultrasound showed ventriculomegaly with periventricular cysts. Brain MRI showed extensive white matter loss and signal abnormality, and some blooming of ependymal surfaces | Positive | Positive (IgG only) | Negative (PCR urine) (No neonatal COVID-19 test) |
| 3 | 02/02/21 | 20 | 32 | Subependymal cysts, parenchymal signal abnormalities, suggestion of polymicrogyria, mild ventriculomegaly, | Ultrasound showed germinal matrix cysts, mineralizing vasculopathy, punctate periventricular echoes and left occipital horn prominence with likely septation. Brain MRI showed ventriculomegaly, particularly of the occipital horns, with horizontal septation on the left, bilateral frontal and parietal periventricular leukomalacia and cysts, periventricular white matter calcification of bilateral frontal lobe, diffuse pachygyria, cortical dysplasia and polymicrogyria | Negative | Positive (IgM and IgG) | Positive (PCR urine) |
| 4 | 05/12/21 | 16 | 36 | White matter signal abnormalities, subcortical and subependymal cysts, mild ventriculomegaly | Ultrasound showed mineralizing vasculopathy and bilateral subependymal cysts. Brain MRI showed bilateral subependymal cysts, T2 white matter hyperintensities, possible punctate calcification, and mild ventriculomegaly | Positive | Positive (IgG only) | Positive (PCR urine) (COVID-19 also positive) |

*Table 1. Fetal MR Findings*

### RESULTS

Three fetuses had imaging features suggestive of CMV with confirmatory post natal urine PCR. One child (patient 2) had a negative neonatal urine PCR for CMV but had imaging findings on fetal MR suggestive of CMV including ventriculomegaly, altered parenchymal signal and periventricular calcifications. This patient's mother suffered from hydrops fetalis early in the pregnancy, possibly from maternal-fetal hemorrhage, treated with fetal transfusion. This complication of pregnancy was attributed to COVID-19. However, it is unclear if the imaging findings on fetal MR were a sequelae of COVID-19 infection, ischemia from hemorrhage/ anemia, CMV, or a combination of causes in this case.

The patient (patient 4) with positive neonatal urine CMV as well as maternal and neonatal COVID-19 demonstrated imaging findings similar to the patients with only CMV infection. Figure 3 demonstrates pre and postnatal imaging of this patient. with CMV COVID-19 coinfection.

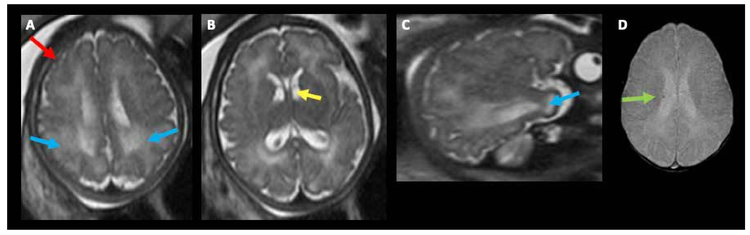


*Figure 3. A, B, C: Prenatal fetal axial and sagittal MR T2 HASTE images at 36 weeks gestation demonstrates parenchymal hyperintensities (blue arrows) and lateral ventricle intraventricular cysts/septations (yellow arrow). There is also suggestion of polymicrogyria of the right frontal lobe (red arrow).*

*D: Postnatal MR axial T2* image at 7 weeks old demonstrates a potential periventricular calcification (green arrow).*

### DISCUSSION

Maternal COVID-19 infection is still not well understood, especially its relationship to other maternal infections. It has been shown that maternal COVID-19 infection can cause an increased risk of preterm delivery[1]. Whether or not COVID-19 can cross the placenta to the fetus is not well agreed upon[2,3]. At our institution we have recently noticed an increase in fetal MR imaging in fetuses with CMV in comparison to prior to the COVID-19 pandemic. It is not clear if this is coincidental or if COVID-19 potentiates other infections in the fetus including CMV infection. Seemingly in our small patient cohort, the imaging findings between fetuses and neonates with maternal CMV COVID-19 co-infection and CMV alone seem to be of a similar severity. Long term neurological outcome analysis would be helpful in the future to identify any imaging and clinical differences in those with CMV only versus CMV COVID-19 coinfection. A potential limitation of this study is that the mothers were for the most part only tested for COVID-19 once during their pregnancy and therefore if not symptomatic the mother may have not been tested, not allowing for identification of some cases. Considering what seems to be an increase in prevalence of CMV at our institution during the pandemic, we suspect some of these mothers were perhaps COVID-19 positive at some point in the pregnancy, leading to possible increased CMV infection risk to the fetus. Future aggregated studies looking at timing of maternal COVID-19 infection, its relationship to CMV serology and imaging, and finally outcome would be helpful.

## Conclusion

- Prenatal CMV diagnosis can be suggested by presence of imaging features such as ventriculomegaly, subependymal cysts, periventricular T2 hyperintensities, calcifications, polymicrogyria, and temporal pole cysts.
- Confirmation can be performed by neonatal urine PCR or maternal amniocentesis.
- CMV in the COVID era raises a number of questions including the potential higher prevalence, and whether COVID-19 potentiates CMV infection in fetuses. Further studies may be needed to recognize patterns.

## References

1. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320. Published 2020 Sep 1. doi:10.1136/bmj.m3320
2. Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020 Jul 14;11(1):3572. doi: 10.1038/s41467-020-17436-6. PMID: 32665677; PMCID: PMC7360599.
3. Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, et al. Vertical Transmission of Coronavirus Disease 19 (COVID-19) from Infected Pregnant Mothers to Neonates: A Review. Fetal Pediatr Pathol. 2020;39(3):246-250. doi:10.1080/15513815.2020.174712

P24521m_102721