Imágenes de Resonancia Nuclear Magnética Cerebral Fetal en infecciones por Citomegalovirus con correlación de imágenes postnatales.
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(Traducción libre: M. Osses)

La Imagen por Resonancia Nuclear Magnética Cerebral Fetal (IRM) es una poderosa herramienta para el diagnóstico de infección congénita sintomática por citomegalovirus que requiere una búsqueda detallada de características concretas. La combinación de anomalías de lóbulo temporal anterior, lesiones de sustancia blanca, y Polimicrogiria es un indicador muy predictivo. La RM fetal puede proporcionar una oportunidad única para detectar quistes temporales anteriores y tabiques de cuerno occipital, como la dilatación de estas áreas puede disminuir más adelante con el desarrollo. anomalías de la migración cortical, anomalías de la materia blanca, displasia cerebelosa, y calcificaciones periventriculares están frecuentemente mejor representados en las imágenes después del parto, pero también puede ser detectado en la RM fetal. Presentamos los resultados de la RM cerebral prenatal observados en Infección congénita por citomegalovirus proporcionando la correlación de imágenes post-natal, destacando la evolución de los resultados en diferentes momentos de la evolución prenatal y postnatal.
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Conclusiones
El CMV es la infección más común adquirida prenatalmente y puede verse en 0,6% -0,7% de todos los nacimientos vivos. La infección puede ser completamente asintomáticos o causar discapacidad neurológica severa permanente. La Resonancia magnética cerebral fetal es una poderosa herramienta en el diagnóstico sintomático de la infección congénita por CMV, con mayor sensibilidad en comparación con prenatal de Estados Unidos. En todos los fetos evaluados para ventriculomegália, microcefalia, o retardo del crecimiento intrauterino, debe llevarse a cabo una búsqueda detallada de las características específicas de la infección por CMV. Una combinación de alteraciones de lóbulo temporal anterior, lesiones de sustancia blanca, y polimicrogiria son especialmente predictivos. RM fetal representa una buena instancia para detectar quistes temporales anteriores y tabiques cuerno occipital, como la dilatación de estas áreas que pueden disminuir o desaparecer más adelante en el desarrollo. Las anomalías corticales de migración, anomalías de la materia blanca, displasia cerebelosa, y calcificaciones periventriculares están a menudo mejor representados en formación de imágenes postnatal pero también se puede detectar en la RM fetal.
Fetal brain magnetic resonance imaging (MRI) is a powerful tool in the diagnosis of symptomatic congenital cytomegalovirus infection, requiring a detailed search for specific features. A combination of anterior temporal lobe abnormalities, white matter lesions, and polymicrogyria is especially predictive. Fetal MRI may provide a unique opportunity to detect anterior temporal cysts and occipital horn septations, as dilation of these areas may decrease later in development. Cortical migration abnormalities, white matter abnormalities, cerebellar dysplasia, and periventricular calcifications are often better depicted on postnatal imaging but can also be detected on fetal MRI. We present the prenatal brain MRI findings seen in congenital cytomegalovirus infection and provide postnatal imaging correlation, highlighting the evolution of findings at different times in prenatal and postnatal developments.

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Introduction

Cytomegalovirus (CMV) is an endemic herpesvirus that is spread by close contact with bodily fluids, with up to 90% of individuals infected by late adulthood. In children and adults, CMV infection is typically asymptomatic or produces a mild, flu-like illness. Special groups, though, are susceptible to severe illness caused by the virus, including immunocompromised patients, newborns (especially when premature), and fetuses. Congenital CMV infection occurs through transplacental transmission, most commonly in women who acquire a primary infection during pregnancy, although transmission during secondary infection can also occur. Congenital CMV infection is seen in approximately 0.6%-0.7% of all live births in industrialized countries, with 11%-13% of those being symptomatic at birth. Clinical findings of congenital CMV infection in the newborn are varied, with more severe features associated with first and second trimester infection. Intrathecal growth restriction, hydrops, thrombocytopenic purpura, jaundice, hepatosplenomegaly, hepatitis, pneumonitis, chorioretinitis, microcephaly, poor tone and suck, sensorineural hearing loss, and seizures have all been described. Outcomes for these newborns are varied as well. Long-term neurologic sequelae are seen in approximately 50% of symptomatic newborns including sensorineural hearing loss, visual impairment, cognitive impairment, seizures, cerebral palsy, and developmental delay. An additional 5%-15% of asymptomatic newborns will develop neurodevelopmental sequelae, most commonly hearing loss, although developmental delay and seizures are also seen. Sensorineural hearing loss due to congenital CMV infection can be unilateral or bilateral and may not be detected with routine newborn screening owing to its often progressive or fluctuating course. It is estimated that congenital CMV infection is responsible for 10%-25% of cases of sensorineural hearing loss diagnosed by 4 years of age.

Serologic screening for CMV infection is not part of routine prenatal or neonatal care in the United States. If performed, maternal primary infection can be established by conversion from IgG-negative to IgG-positive status, or positive IgM with low IgG. Fetal infection can be confirmed with positive viral culture or polymerase chain reaction (PCR) of amniotic fluid. In the newborn, confirmation of congenital CMV infection with blood, urine, or saliva viral culture or PCR must be
performed within the first 3 weeks of life to exclude postnatal infection.\textsuperscript{5} It is possible to perform PCR testing on the dried blood spot of the newborn screening card later.\textsuperscript{9}

Brain abnormalities seen on prenatal ultrasound (US) are often the first indication of congenital CMV infection. Ventriculomegaly is most commonly seen, with microcephaly and periventricular calcification also commonly noted.\textsuperscript{10} Other features that can be detected with targeted US include subependymal cysts, intraventricular synchia, white matter hyperechogenicity, callosal hypoplasia, lenticulostriate vasculopathy, sulcation and gyral abnormalities, and cerebellar and cisterna magna anomalies.\textsuperscript{11} When 1 or more of these features is detected, magnetic resonance imaging (MRI) is often pursued for more detailed evaluation, as the addition of MRI increases the sensitivity and positive predictive value for the diagnosis of symptomatic congenital CMV infection.\textsuperscript{10,12} New developments in prenatal and postnatal antiviral treatments add to the importance of accurate and timely diagnosis.

In this article, we review the prenatal brain MRI findings seen in congenital CMV infection and provide postnatal imaging correlation, highlighting the evolution of findings at different times in prenatal and postnatal development (Box 1).

**Fetal Brain MRI Features of Congenital CMV**

As for most fetal MRI examinations, multiplanar T2-weighted images (eg, single-shot fast spin echo or half-fourier acquisition single-shot turbo spin-echo [HASTE]) are the workhorse for structural evaluation of the brain. Steady-state free precession images (eg, fast imaging employing steady-state acquisition [FIESTA] or true fast imaging with steady-state precession [TruFISP]) can be a useful adjunct for structural evaluation. T1-weighted and gradient-recalled echo images aid in detection of hemorrhage or calcification. Fetuses as young as 18 weeks of gestation can be imaged, although the normal lack of sulcation at this point in development limits the ability to detect migration abnormalities associated with congenital CMV infection. On the contrary, a detailed third trimester fetal MRI may obviate the need for immediate postnatal MRI.

**Intracranial Calcifications**

Periventricular calcification is considered a hallmark of congenital CMV infection and a predictor of developmental delay, seen in 34%-70% of cases.\textsuperscript{13} Although more easily depicted with targeted prenatal US,\textsuperscript{10} intracranial calcification can be seen on fetal MRI as low T2 or high T1 signal. Careful evaluation is needed to detect subtle, punctate foci of signal abnormality along the ventricular walls. Calcification can also occur in the basal ganglia, as linearly arrayed lenticulostriate vasculopathy or more puncate foci, and in the brain parenchyma, but it is usually more fine and difficult to detect on fetal MRI. The lack of obvious intracranial calcification on fetal MRI, then, should not dissuade the reader from the diagnosis of congenital CMV. Postnatal MRI with high-resolution susceptibility-weighted images, computed tomography, or US can be confirmatory (Figs. 1 and 2).

**Cortical Migrational Abnormalities**

A spectrum of cortical migration abnormalities can be seen in congenital CMV infection, largely depending on the timing of in utero infection. If the infection occurs before 16-18 weeks of gestation, lissencephaly results.\textsuperscript{14} If the infection occurs between 18 and 24 weeks of gestation, polymicrogyria

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**Box 1–Summary of Fetal and Postnatal MRI Findings in Congenital CMV Infection.**

<table>
<thead>
<tr>
<th>Imaging Feature</th>
<th>Specific Details</th>
<th>Fetal MRI</th>
<th>Postnatal MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>Usually detected on prenatal US, which may be an indication for fetal MRI</td>
<td>May detect microencephaly as well</td>
<td>More easily detected with susceptibility-weighted imaging, or CT or US imaging</td>
</tr>
<tr>
<td>Calcification</td>
<td>Most often periventricular</td>
<td>Low T2 or high T1 signal, which is often subtle</td>
<td>Variable, often moderate to severe</td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td>May be only indication on prenatal US for fetal MRI</td>
<td>Often mild to moderate</td>
<td>Decrease in size and conspicuity with age, consider high-resolution SSFP</td>
</tr>
<tr>
<td>Periventricular cysts</td>
<td>Especially anterior temporal lobes</td>
<td>Temporal polar lesions highly predictive of CMV infection</td>
<td>Decrease in size and conspicuity with age, consider high-resolution SSFP</td>
</tr>
<tr>
<td>Intraventricular septa</td>
<td>Especially occipital horns</td>
<td>Cystic dilation of occipital horns</td>
<td></td>
</tr>
<tr>
<td>Cerebellar hypoplasia or dysplasia</td>
<td>Sometimes with cerebellar white matter abnormalities</td>
<td>Difficult to detect unless severe</td>
<td>Mild dysplasia and white matter abnormalities well depicted</td>
</tr>
<tr>
<td>Cortical migration anomalies</td>
<td>Frontal or perisylvian polymicrogyria or pachygyria</td>
<td>Smudgy or thickened cortex on T2, better seen in third trimester</td>
<td>More easily seen, especially after myelination has occurred</td>
</tr>
<tr>
<td>White matter abnormalities</td>
<td>Periventricular high T2 signal, which may sometimes be cystic</td>
<td>May be extensively involved</td>
<td>High T2 signal may be more conspicuous with age, but appears less extensive</td>
</tr>
</tbody>
</table>

CT, computed tomography; SSFP, steady-state free precession.
predominates. Fetuses affected in the third trimester usually have a normal gyral pattern. Schizencephaly and cleft cortical dysplasia have been occasionally reported in cases of congenital CMV infection as well.\textsuperscript{15} Frontal and perisylvian polymicrogyria is the most commonly observed migrational abnormality,\textsuperscript{15} with fetal MRI much better suited for detailed cortical evaluation than US. A smudgy and sometimes thickened appearance of the dark cortical ribbon is noted on T2-weighted images, usually in conjunction with a poorly formed gyral pattern. These findings are more easily detected in the third trimester when a more mature sulcation pattern is expected. Likewise, polymicrogyria is more clearly shown on postnatal MRI than prenatal examinations. Pachygyria, as a less severe expression of lissencephaly, is similarly shown to best advantage later in gestation. In these cases, a smooth or only mildly wavy cortical surface is seen, especially in the frontal lobes, at a gestational age when a more robust gyral pattern should be observed (Figs. 3 and 4).

**Anterior Temporal Lobe Abnormalities**

Abnormal development of the anterior temporal lobe seen on fetal MRI, sometimes termed "polar temporal lesions," is especially predictive of congenital CMV infection.\textsuperscript{16} Swelling and excessive T2 hyperintensity in the anterior temporal white matter, anterior temporal cysts separated from the ventricle by a thin septation, and mild dilation of the temporal horn itself have been described.\textsuperscript{17} The dilated temporal horn may reflect hippocampal dysplasia reported on postnatal MRI examinations,\textsuperscript{17} but detailed evaluation of hippocampal morphology is usually beyond the resolution of fetal MRI. There may also be decreased volume of the temporal lobes compared with unaffected fetuses.\textsuperscript{18} These

![Figure 1](image-url)
anterior temporal lobe features can be seen alone or, more often, in combination and are commonly bilateral. These findings become less conspicuous on postnatal imaging and may nearly completely resolve over time, highlighting the importance of their recognition on fetal MRI examinations (Fig. 5).

Anterior temporal lobe abnormalities are much better evaluated with fetal MRI compared with fetal US, comprising much of the “added value” seen with obtaining fetal MRI in cases of suspected congenital CMV infection. In the experience of Doneda et al with 38 cases of confirmed congenital CMV infection, polar temporal...
lesions were the most frequent pathologic finding on fetal MRI, detected in 14 cases (36.8%). None of these lesions, however, were detected with fetal US. Postnatally, detection of anterior temporal lobe abnormalities may point to congenital CMV infection when not previously considered. This is especially true in cases of unexplained developmental delay and hearing loss.

Although highly associated with congenital CMV, anterior temporal lobes cysts in children can be seen in other diseases such as congenital muscular dystrophy, megalencephalic leukoencephalopathy with subcortical cysts, non-megalencephalic leukoencephalopathy with subcortical cysts, and Aicardi-Goutieres syndrome.20 The finding of microcephaly, periventricular calcifications, parietal white matter abnormalities, or cortical malformations in addition to anterior temporal lobe cysts points to CMV rather than other possibilities.

**Ventricular Abnormalities**

After anterior temporal lobe abnormalities, ventriculomegaly is the second most common fetal MRI feature in confirmed cases of congenital CMV infection.12 Although nonspecific, moderate to severe ventriculomegaly can be seen in as many as 45% of postnatally imaged cases of congenital CMV infection.13 With fetal imaging, ventriculomegaly tends to be more mild to moderate in our experience. Often, ventriculomegaly is the only second trimester US feature that prompts fetal MRI (Fig. 3).

Ventricular septations are also nonspecific but often seen in cases of congenital CMV infection. Thin strands of tissue crossing the ventricles are typically depicted in the occipital horns on axial T2-weighted images. These septations may cause cystic dilatation of the occipital horns in utero but become less pronounced after birth, again highlighting the utility of high-resolution fetal imaging in these patients.
Postnatally, great attention to detail is needed to detect these subtle septations if the associated dilatation has resolved. High-resolution thin-section steady-state free precession images may be useful (Fig. 6).

White Matter Abnormalities
Postnatally, several patterns of white matter abnormalities have been associated with congenital CMV infection in children presenting with static encephalopathy of unknown cause, including multifocal white matter lesions predominately involving the parietal lobes, multifocal white matter lesions with polymicrogyria, and diffuse white matter abnormalities with polymicrogyria. These white matter lesions appear as T2 hyperintensity, most easily detected after some degree of myelination has occurred. Given the inherent T2 hyperintensity of the white matter on fetal MRI, though, detection of white matter abnormalities can be difficult. Asymmetry may be helpful, if present. A thin strip of lower signal in the immediate periventricular or subcortical white matter, a feature described postnatally, can also be a useful sign on fetal MRI. Although more conspicuous postnatally, white matter abnormalities may appear more extensive on fetal MRI compared with later in development. This apparent regression of leukoencephalopathy has also been described in a case report of serial postnatal MRIs in a child (Figs. 4, 7, and 8).

Cerebellar Hypoplasia and Dysplasia
Barkovich et al reported on cerebellar hypoplasia in 8 of 11 children with congenital CMV infection, noting that most other processes that disrupt neuronal migration spare the cerebellum. Cerebellar hypoplasia and dysplasia have also been described on fetal MRI but are seen in only a minority of cases. Similar to prenatal US, cerebellar hypoplasia can be established by comparing the transverse
Figure 6 Abnormalities seen on prenatal US prompted fetal MRI at 37 weeks of gestation. (A, B) Axial T2-weighted MR images show dilated atria and occipital horns of the lateral ventricles with thin septations (arrows). (C) Axial T2-weighted postnatal MR image performed on day 1 of life and (D) axial T2-weighted MR image obtained at 7 months of age demonstrate decreasing conspicuity of the occipital cysts with thin septations over time (arrows). Notice polymicrogyria in the bilateral frontal and perisylvian regions on fetal MRI, with poor gyral formation, more easily seen by 7 months of age.

Figure 7 Fetal MRI performed at 35 weeks of gestation for ventriculomegaly on prenatal US. (A) Sagittal T2-weighted fetal MR image and (B) sagittal T1-weighted postnatal MR image at day 1 of life reveal periventricular white matter changes (arrows), which become less extensive on (C) sagittal T2-weighted MR image performed at 16 months of age. Notice also the decreasing conspicuity of the occipital cysts (arrowheads) with thin septations over time.
Figure 8  Fetal MRI performed at 31 weeks of gestation for ventriculomegaly on prenatal US. (A) Parasagittal T2-weighted fetal MR image and (B) sagittal T2-weighted postnatal MR image performed at 5 months of age show white matter changes including T2 hyperintensity (arrows) and cyst formation (arrowheads), more easily seen on postnatal imaging. Occipital white matter volume loss is evident on prenatal and postnatal scans (dashed arrows).

Figure 9  Fetal MRI performed at 30 weeks of gestation for intrauterine growth restriction. (A) Axial and (B) coronal T2-weighted fetal MR images and (C) axial and (D) coronal T2-weighted postnatal MR images performed at 5 days of age show bilateral areas of increased T2 signal or cystic changes within the cerebellar hemispheres (arrows) indicating cerebellar dysplasia.
Severe cerebellar hypoplasia with focal white matter abnormalities may be easily detected on fetal MRI, but more subtle areas of cerebellar dysplasia are more clearly depicted on postnatal MRI (Figs. 9, 10, and 11).

Microcephaly and Microencephaly
Microcephaly, defined as a small calvarial size, and microencephaly, defined as small cerebral hemisphere size, are seen in up to a quarter of cases of congenital CMV infection. Biparietal diameter is typically evaluated on a preceding US examination, and microcephaly may be an indication for the fetal MRI. Microencephaly may be more clearly depicted on fetal MRI compared with US, owing to better visualization of the subarachnoid spaces. Normative biometric values for fetal brain MRI are available for reference if measurements are required.

Clinical Perspective
MRI provides superior image quality of the fetal brain and allows for detailed evaluation of possible features of congenital CMV infection. In already suspected cases, MRI findings may build a case for prenatal or postnatal antiviral therapy or possibly termination of pregnancy in severely affected fetuses. Findings on fetal brain MRI may also be the first clue to making the diagnosis.

A study by Doneda et al correlated prenatal US and MRI findings with CMV infection-related neurologic outcomes in 30 children. Fetal MRI did show higher sensitivity than US in predicting symptomatic infection (83% vs 33%). However, both modalities showed low positive predictive values (36% with MRI vs 29% with US). Another study of fetal US and MRI in 38 cases of congenital CMV infection by Picone et al showed that MRI added important details, especially regarding detection of gyrational anomalies, cerebellar hypoplasia, and

Figure 10  Fetal MRI obtained at 30 weeks of gestation for bilateral ventriculomegaly and cerebellar hypoplasia. (A) On US performed at 28 weeks of gestation, the transverse cerebellar diameter (between calipers) measures 3 weeks behind gestational age. (B) On axial T2-weighted fetal MR image, the transverse cerebellar diameter (arrowheads) is below normal range as well. (Color version of figure is available online.)

Figure 11  Fetal MRI acquired at 31 weeks gestation for ventriculomegaly and cerebellar hypoplasia seen on fetal US. (A) US performed at 25 weeks of gestation shows a small transverse cerebellar diameter (between calipers) for gestational age. Sagittal T2-weighted fetal MR image (B) and sagittal T2-weighted postnatal MR image (C) obtained at 5 months of age reveal brainstem (arrows) and vermis (arrowheads) hypoplasia well seen on these prenatal and postnatal sagittal midline images. (Color version of figure is available online.)
white matter abnormalities. In both of these studies, a negative fetal brain MRI finding was reassuring for a good clinical outcome. Similarly, a third study by Lipitz et al suggested generally good outcomes if both fetal US and MRI examination results were normal, with some cases of partial hearing loss still seen.

Similar to the fetal imaging, postnatal MRI is superior to US for detecting brain abnormalities in documented cases of congenital CMV infection and may play a role in predicting the neurodevelopmental outcomes in these children. Recently, Capretti et al evaluated the role of brain US and MRI in 40 neonates with congenital CMV infection. In cases with normal neonatal brain MRI finding, there was very high likelihood for normal psychomotor and auditory development. Conversely, an abnormal brain MRI finding, even when the US finding was normal, suggested a high likelihood of sensorineural hearing loss or developmental delay or both. A study by Manara et al of brain MRIs in 14 older infants and children identified ventriculomegaly, migration disorders, and hippocampal dysplasia as specific features that may be associated with more severe impairment.

Prenatal therapy with CMV-specific hyperimmune immunoglobulin is controversial, with a recent phase 2 clinical trial study referring earlier claims of improved outcomes. Treatment in the neonatal period is more established and is instituted in infants with evidence of brain involvement including sensorineural hearing loss as well as other serious end-organ disease. Screening of asymptomatic, at-risk newborns is also suggested, including preterm and small for gestational age infants. Moreover, 6 weeks of intravenous therapy with ganciclovir began within the first month of life has been shown to improve hearing or maintain normal hearing in most infants. These children may also show fewer developmental delays in childhood. Oral therapy with its produg, valganciclovir, has also recently been shown to improve hearing and neurodevelopmental outcomes, with a modest benefit of 6 months of therapy compared with 6 weeks. No vaccine for CMV is yet available, but vaccine development is an active area of research.

Conclusions

CMV is the most common prenatally acquired infection and can be seen in 0.6%-0.7% of all live births. Infection may be completely asymptomatic or cause severe lifelong neurologic impairment. Fetal brain MRI is a powerful tool in the diagnosis of symptomatic congenital CMV infection, with greater sensitivity compared with prenatal US. In any fetus evaluated for ventriculomegaly, microcephaly, or intrauterine growth restriction, a detailed search for specific features of congenital CMV infection should be undertaken. A combination of anterior temporal lobe abnormalities, white matter lesions, and polymicrogyria is especially predictive. Fetal MRI may provide a unique opportunity to detect anterior temporal cysts and occipital horn septations, as dilation of these areas may decrease later in development. Cortical migration abnormalities, white matter abnormalities, cerebellar dysplasia, and periventricular calcifications are often better depicted on postnatal imaging but can also be detected on fetal MRI.

References