Imaging patterns in fetal CNS infections

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Authors: R. T. Popa¹, C. Fayard², E. Blondiaux², J.-M. Jouannic², H. Ducou le Pointe², C. Garel²; ¹Cluj-Napoca/RO, ²Paris/FR
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Learning objectives

To illustrate the imaging spectrum of fetal CNS infectious lesions, with emphasis on MRI findings. To outline the advantages and limitations of each technique. To describe the indications and results based on a series of 132 patients with confirmed toxoplasmosis or CMV infection.
Background

Congenital viral infections are very common conditions worldwide and may cause brain damage. The Cytomegalovirus [CMV] and the Toxoplasma gondii are the most common infectious agents that are known to be responsible for brain damage.

The imaging appearance varies depending on the pathogenic agent and the gestational age at exposure. [1]

US is the primary imaging modality and makes it possible to evaluate the placenta and the whole fetus. MRI is also widely used in the setting of congenital infection in order to search for cerebral lesions. Both modalities are complementary:

- MRI is more accurate than US in the analysis of white matter and cortical abnormalities. Moreover, the temporal lobes are usually better analyzed with MRI than with US.

- Calcifications are well depicted with US and may be completely overlooked by MRI, even when using gradient echo sequences. [2,3]

There is still no consensus regarding the indications for fetal MRI in congenital infections. Moreover the prognosis of certain lesions is still uncertain.
Based on our personal experience (Trousseau Hospital, Paris) of a series of 132 patients with confirmed maternal infection (117 CMV, 15 Toxoplasma gondii) and the analysis of pathological cases of this series, the main fetal cerebral findings in CMV and toxoplasma infections are displayed. These consisted in the following lesions: intracranial calcifications, lenticulostriate vasculopathy (both lesions being depicted with **US only**), polymicrogyria, white matter abnormalities (both lesions being **better depicted by MRI** with diagnostic difficulties regarding the white matter lesions), microcephaly, ventricular dilatation, pseudocysts (all these lesions being depicted by **US and MRI**).

**CMV**

The imaging appearance varies depending on the gestational age at exposure.

It is known that CMV shows tropism for neural stem cells in the fetal brain, which appear to be the predominant cell type affected during fetal infection. It inhibits the transformation of neuronal precursors into neurons and induces apoptosis of infected cells, which may have potential effects in brain size and maturation. Among other pathogenic mechanisms CMV also interferes with the normal neuronal migration. [4]

Therefore, fetal infections occurring during the first and early second trimester can lead to severe microcephaly and gyration disorders (lissencephaly), associated with ventricular dilatation. These abnormalities are often depicted by US. CMV infection may also cause cerebellar hypoplasia [5]

If fetal infection occurs after 26-28 weeks of gestation, the predominant imaging findings are inflammatory lesions of the white matter [5].

**Microcephaly** (Fig 1.)

- rarely isolated, usually associated with polymicrogyria and opercular dysplasia -US diagnosis is based on head circumference measurements, MRI allows true cerebral measurements

**Polymicrogyria** (Fig. 3, 6 and 7)

- overfolding of the cortex

- the diagnosis is possible with US if US is performed early (22-28 GW). This finding is usually easily demonstrated by MRI.

**Cerebellar hypoplasia** (Fig.1)
- diagnosed by evaluation of the transverse cerebellum diameter (US and MRI) -
cerebellar hypoplasia seems to be more pronounced the earlier the infection occurs

- the vermis is more accurately measured on MRI (height, surface)

**Intracranial calcifications** (cerebellar, periventricular, parenchymal) (Fig. 3 and 4)

- are considered the hallmark of fetal infection (not only CMV), especially when associated
  with microcephaly

- secondary to necrosis

- punctuated (may be present in any part of the brain) or linear ("en plaque", usually
  periventricular)

- better depicted by US (no acoustic shadow) than MRI. Areas of calcified necrosis may
  appear as T1 hyper intensities and T2 hypointensities.

**Ventriculomegaly** (Fig. 1 and 7)

- common feature (18% of infected fetuses)

- different degrees of severity

- CMV infection must be systematically searched for in case of ventriculomegaly, even
  if it is isolated.

**Periventricular pseudocysts** (Fig. 3, 6 and 7)

- predominantly facing occipital and temporal ventricular horns (sometimes better
  depicted with MRI, particularly temporal pseudocysts)

- result from necrosis or hemorrhage within the germinal matrix

- may also be observed in chromosomal and metabolic diseases but are very suggestive
  of CMV infection when they are located in the occipital and temporal lobes

**Intraventricular synechiae**

- related to ventriculitis

- may be very difficult to differentiate from subependymal cysts

- better visualized with US than MRI

**Hyperechogenity of the germinal matrix** (Fig. 4)

- related to CMV tropism for cells with high mitotic activity
**Lenticulostriate vasculopathy** (Fig.5)

- not to be confused with linear calcifications

- results from accumulation of basophilic deposits in the vessels walls- depicted only with US, overlooked by MRI

**White matter abnormalities** (Fig.2)

- not visible on US, unless in very severe white matter involement

- abnormal signal intensity of the white matter with increased ADCs

[5], [6],[7]

**T. gondii**

As for CMV infection, congenital toxoplasmosis is also more severe the earlier transplacental passage of the parasite occurs. In early seroconversion (before 20 weeks of gestation), **microcephaly** and **ventricular dilatation** are signs of severe neurological involvement. **Hydrocephalus** is attributed to aqueductal stenosis or obstruction due to periaqueductal inflammation and necrosis. [8]

One of the T. gondii neuropathogenic mechanisms is vasculitis and it leads to parenchymal necrosis and focal inflammation. [8] If the cortex is involved, **polymicrogyria** can be observed, while the involvement of the white matter leads to **cavitations** +/- **calcifications** (Fig. 8).

After 30 weeks of gestation, the cerebral findings are less severe. Late transmission, however, can also lead to severe brain involvement, as published in a recent study. [9]

Most of the cerebral lesions caused by T. gondii are identifiable in US. MRI has the slight advantage to better depict some cavitary or polymicrogyric lesions that may be overlooked by US. [5]

Chorioretinitis is a very common complication in infected neonates (85%), but it cannot be diagnosed in fetuses.
Fig. 2: Maternal CMV seroconversion during the first trimester. 31 GW: Coronal (a), axial (b) and sagittal (c) T2-weighted images showing increased signal intensity of the periventricular white matter, with increased diffusion coefficients (d).

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**Fig. 1:** Maternal CMV seroconversion. US findings: IUGR, hyperechoic bowel loops, markedly decreased cerebellar and cerebral biometric parameters with abnormal gyration. MR at 22+2 weeks: Marked micrencephaly. Axial T2-weighted image (a) showing absence of sylvian fissure and ventriculomegaly. Sagittal T2-weighted image (b) showing marked vermian hypoplasia. Coronal T2-weighted image (c) displaying a large parietooccipital porencephalic cavity displacing the right ventricle. Axial T1-weighted image (d) showing hyperintense cortex surrounding the porencephalic cavity, suggestive of laminar necrosis.

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**Fig. 3:** CMV seroconversion at about 10 GW. US at 24 GW: microcephaly with multiple periventricular and parenchymal hyperechoic foci, consistent with calcifications (arrow heads), occipital subependymal pseudocyst facing one occipital horn (b) and bilateral opercular dysplasia (arrows) (absence of sylvian fissures). The cerebral surface is irregular, in keeping with polymicrogyria.

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Fig. 4: Maternal CMV infection with fetal US demonstrating IUGR and numerous cerebral abnormalities. 33 GW: sagittal (a,c) and coronal (b) US images showing periventricular and parenchymal calcifications (arrow heads). The germinal matrix thickened and slightly heterogeneous (arrow). Sagittal T2-weighted images (d): the calcifications depicted on US are not visible with MRI. The ventricular border is irregular, in relation with ependymal damage.

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**Fig. 5:** CMV infection. 32 GW: coronal views at the level of the basal ganglia. Hyperechogenicity of the lenticulostriate vessels (CMV vasculopathy).

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Fig. 6: CMV infection. Microcephaly. US at 28 GW: Subependymal pseudocyst (a) (confirmed by neuropathological examination) facing the occipital horn. It is impossible to differentiate such a pseudo cyst from a ventricular synechia. Coronal view (b) showing overfolding of the cortical ribbon of the frontal lobes and enlarged pericerebral space. Axial view at the level of the thalami (c): opercular dysplasia of the deep hemisphere.

Fig. 7: CMV infection. US at 28 GW: Coronal (a) and sagittal (b) views. Ventricular dilatation with subependymal occipital pseudo-cyst (b). Reduced thickness of the cerebral parenchyma. Hyperechogenicity of the cerebral surface suggesting laminar necrosis or extended calcifications (a). These findings were associated with diffuse polymicrogyria and gyration abnormalities.

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Fig. 8: Toxoplasmosis seroconversion. Patient referred for US findings in keeping with fetal infection (ascites, hyperechoic bowel loops, hepatosplenomegaly and disseminated cerebral microabcesses). US at 32 GW: Coronal ultrasonographic images at the frontal (a) and parieto-occipital (b) levels showing multiple hyperechoic lesions disseminated in the cerebral parenchyma. Sagittal (a) and axial (b) T2-weighted images showing increased signal intensity of the white matter. The microabcesses appear T2 hypointense (arrow heads) and T1 hyperintense. Most of them are overlooked by MRI.

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Conclusion

The imaging findings described above are highly suggestive of fetal infection, particularly when several findings are associated. However, it must be kept in mind that they can also be observed in certain recessive autosomal syndromes, such as pseudo-TORCH diseases (e.g. Aicardi-Goutieres syndrome).

US is a valuable imaging tool, as it can depict most of the infectious fetal brain lesions. Fetal MRI is an important adjunct to sonography. With MRI, cortical involvement and white matter damage are usually better visualized than with US. In the setting of fetal infection, US and MRI are complementary imaging modalities and should be used together, making it possible to improve prognostic evaluation and therefore prenatal counseling.

In CMV infection, there is still no consensus regarding the appropriate time for performing fetal cerebral MRI. In case of a major malformation clearly demonstrated by US, MRI does not provide any relevant additional information.

In case of toxoplasma infection, the role of MRI is still debatable.

The prognosis of certain lesions remains unclear. It is well documented that microcephaly and gyration anomalies carry a poor prognosis, while other signs of viral cerebral involvement (calcifications, ventriculomegaly, ventricular synechiae, periventricular cysts and lenticulostriate vasculopathy) have uncertain later neurological impact. The prognostic of isolated white matter injury is still unknown.
Personal Information

Roxana Tania Popa MS.

Department of Radiology,
Cluj Emergency County Hospital (Spitalul Clinic Judetean de Urgenta Cluj),
Cluj-Napoca, Romania

E-mail: roxanatania@yahoo.com
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