

## Cortical maturation assessed by MRI in unaffected/mildly affected fetuses with cytomegalovirus infection

Hawkins-Villarreal A, Moreno-Espinosa A. L, Castillo K, Hahner N, Martinez-Portilla R. J, Picone O, Mandelbrot L, Simon I, Gratacós E, Goncé A, Eixarch E. BCNatal - Fetal Medicine Research Center (Hospital Clínic and Hospital Sant Joan de Déu). Universitat de Barcelona, Barcelona, Spain; and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain., Barcelona, Spain

### Objective

This study aimed to comprehensively assess the pattern of cortical maturation by MRI in fetuses with unaffected and mildly affected CMV infection and establish whether there were differences compared to a group of healthy controls.

### Methods

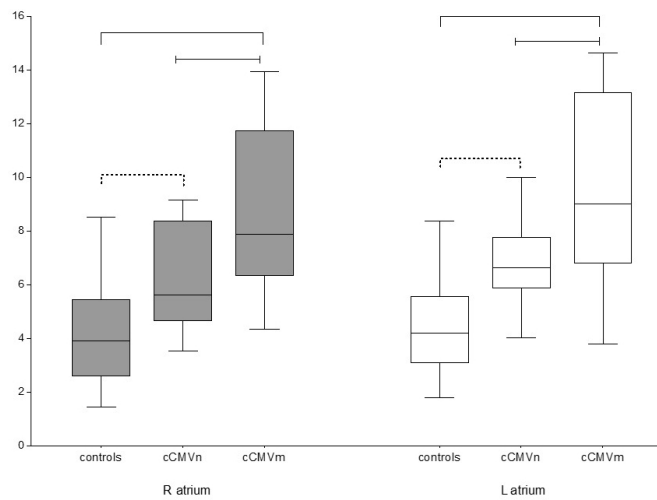
Twenty-four CMV-infected fetuses (7 unaffected, 17 mildly affected) and 24 healthy controls between 27 and 36 weeks of gestation with fetal MRI were included. Fetuses were considered unaffected or mildly affected according to prenatal neuroimaging findings by US/MRI. We compared the fetal sulci depth, Sylvian fissure depth, Sylvian fissure angle and cortical maturation grading of specific areas between study groups. Regression, parametric trend and intraclass correlation analysis were performed.

### Results

Compared to controls, in the CMV-infected fetuses we observed bilaterally a significantly larger median (IQR) width of the lateral ventricles, significantly decreased parietooccipital-sulcus and calcarine-sulcus depth,  $p < 0.001$ ; and a significantly larger upper and lower Sylvian-fissure-angle,  $p < 0.001$ . In addition, that the infected fetuses had a significantly lower cortical-grading in temporal-area, parietal-area, parietooccipital-sulcus, and calcarine-sulcus, compared to the healthy fetuses ( $p < 0.05$ ). These differences persist when adjusting for gestational age, ipsilateral atrium, fetal gender and considering being small for gestational age as a confounding/interacting factor.

### Conclusion

CMV-infected fetuses with mild involvement showed an underdeveloped cortical maturation compared with healthy controls. These results suggest that congenital CMV infection, even in unaffected and mildly affected fetuses, which are typically considered of good prognosis, could be related to altered brain cortical structure. Further research is warranted to better elucidate its correlation with neurodevelopmental outcomes.



**Figure.** Boxplot graph of lateral ventricular width in right and left brain hemispheres in study groups.  $p$  value estimated with the Kruskal-Wallis equality of population rank test, adjusted for gestational age at MRI. \* $p < 0.05$ , (controls: healthy fetuses, cCMVn: unaffected CMV-infected fetuses, cCMVm: mildly affected CMV-infected fetuses). R: right, L: left.

**Table.** Cortical development parameters between study groups.

Characteristic	Controls ** n = 24	cCMVn n = 7	cCMVm n = 17	$p^*$ value	$p^{\dagger}$ value
<b>Right hemisphere ^</b>					
Insula (mm)	29.7 (28.3 - 30.9)	29.4 (28.2 - 31.4)	29.9 (28.8 - 31.5)	0.67	0.69
Sylvian fissure (mm)	15.9 (14.7 - 17.1)	15.4 (13.7 - 16.2)	15.8 (15.1 - 17.1)	0.46	0.92
Parieto-occipital sulcus (mm)	15.9 (13.5 - 17.3)	12.7 (11.9 - 13.3)*	12.5 (11.3 - 13.8) <sup>†</sup>	<b>0.002</b>	<b>&lt; 0.001</b>
Cingulate sulcus (mm)	4.76 (4.15 - 6.52)	4.32 (4.04 - 5.17)	4.77 (4.03 - 5.61)	0.44	0.61
Calcarine sulcus (mm)	17.5 (16.1 - 18.7)	15.6 (14.7 - 16.9)*	15.4 (13.9 - 16.0) <sup>†</sup>	<b>0.015</b>	<b>&lt; 0.001</b>
Upper Sylvian fissure angle (°)	42.8 (35.8 - 45.8)	41.6 (33.5 - 58.6)	50.1 (40.4 - 65.5) <sup>†</sup>	0.71	<b>0.012</b>
Lower Sylvian fissure angle (°)	41.6 (34.4 - 49.2)	42.6 (38.6 - 49.1)	50.7 (45.8 - 64.6) <sup>†</sup>	0.79	<b>0.009</b>
<b>Left hemisphere ^</b>					
Insula (mm)	29.5 (28.5 - 30.7)	29.4 (28.2 - 31.9)	29.4 (29.0 - 31.2)	0.90	0.94
Sylvian fissure (mm)	16.5 (15.6 - 17.8)	16.1 (14.7 - 17.4)	16.1 (15.2 - 17.6)	0.77	0.95
Parieto-occipital sulcus (mm)	16.0 (13.3 - 17.5)	13.1 (10.1 - 14.4)*	11.6 (10.8 - 12.4) <sup>†</sup>	<b>0.004</b>	<b>&lt; 0.001</b>
Cingulate sulcus (mm)	4.82 (4.02 - 6.57)	4.59 (3.90 - 5.40)	4.79 (3.84 - 5.51)	0.61	0.53
Calcarine sulcus (mm)	16.7 (15.6 - 18.9)	15.4 (14.2 - 15.9)*	14.6 (14.1 - 15.5) <sup>†</sup>	<b>0.018</b>	<b>&lt; 0.001</b>
Upper Sylvian fissure angle (°)	40.9 (34.2 - 45.8)	45.3 (40.1 - 59.5)	51.0 (43.1 - 61.3) <sup>†</sup>	0.11	<b>&lt; 0.001</b>
Lower Sylvian fissure angle (°)	42.2 (38.8 - 46.9)	40.7 (34.8 - 48.9)	54.6 (46.6 - 61.9) <sup>†</sup>	0.54	<b>&lt; 0.001</b>

Data are presented as median (IQR: interquartile range: p25-p75).  $p$  value ( $< 0.05$ ) determined with the Kruskal-Wallis equality of populations rank test and adjusted by ipsilateral atrium and gestational age at MRI, and SGA as a confounding factor compared to controls. \* $p$  value between healthy controls vs. cCMVn. <sup>†</sup> $p$  value between healthy controls vs. cCMVm. ^ Variables normalized by BPD: biparietal diameter and multiplied by 100. cCMVn: unaffected cytomegalovirus infected fetuses. cCMVm: mildly affected cytomegalovirus infected fetuses. \*\*Controls: healthy fetuses.