

Do maternally produced cytokines contribute to fetal neuroinflammation? MR perspectives

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Objectives: Neonatal hypoxia-ischemia (H/I) and/or infections are the main etiopathogenic factors leading to perinatal cerebral palsy. Both are suspected to mediate part of their deleterious effects through the activation of inflammatory pathways and cytokines production. Proinflammatory cytokines, especially interleukin (IL)-1, are thought to have neurotoxic effects on the developing brain. Before using any anti-inflammatory agent to attempt neuroprotection of the neonate, we evaluated whether the cytokines found in the neonatal brain exposed to lipopolysaccharide (LPS) and/or H/I are purely from fetal/neonatal origin or whether the maternal immune system provides an additional contribution. We determined whether maternally-produced cytokines are transferred to the fetal nervous system with contrast-enhanced MRI.

Methods: Studies were performed on a Lewis rat model of prenatal inflammation that mediates the development of brain damage as previously described^{1,2}. Anesthetized animals (isoflurane 1%) were imaged in the dorsal decubitus position using a small-animal 7T MRI system at gestational day 17 (G17). A fast spin-echo pulse sequence (TR/TE_{eff}: 2000/12 ms, 8 echoes, FOV: 6 x 5 cm², matrix: (256)², NA: 8, 20 slices of 1.5 mm) was used to localize the fetus and fetal organs (Fig 1). A bolus of Gd-DTPA (500 µl) was then injected i.v. (tail vein) with simultaneous and continuous monitoring by T₁-weighted images (TR/TE: 197/2.5 ms, FOV: 6 x 5 cm², matrix: (128)², α: 30°, NA: 4, 20 slices of 1.5 mm) for a time period of 60 min. The pregnant rat was then injected every 12 hours either with LPS or saline (controls) until G20 when the MRI procedure was repeated. After imaging, placentas were harvested, stained with hematoxylin/eosin and analysed to determine the histological correlates of LPS-induced inflammation.

Results: We observed that the contrast agent was rapidly distributed in the placenta in both mid and late gestation in control dams (Fig 2a). In LPS-treated dams, the placenta perfusion was decreased or completely absent (Fig 2b). This new insight into the effect of LPS on the placenta was later confirmed by histological tissue analysis, which clearly showed the damage induced to the placenta by inflammation. There was also a small but detectable signal enhancement in the fetuses. The placental permeability to the contrast agent was dependant on the gestational age, with an increased permeability towards the end of gestation as compared to mid-gestation. This finding could reflect the transfer of cytokines to the fetus as confirmed using radiolabeled IL-1β injected to the pregnant rat.

Conclusion: The results suggest that maternally produced cytokines could be transferred to the fetus and could thus participate to the fetal brain damage leading to cerebral palsy. As observed using MRI, radiolabeled cytokines and histology, the decrease in placental perfusion combined with cytokine transfer might account for the brain damage. Those deleterious effects of inflammation will be targeted by potential neuroprotective treatment (e.g., anti-inflammatory molecule). Further studies should include a more precise MR image analysis of targeted fetal organs and the follow-up of the newborn pups.

1. Girard S, Kadhim H, Beudet N et al. Neuroscience, In press, 2008
2. Girard S, Kadhim H, Larouche A et al. Cytokine, 43(1): 54-62, 2008

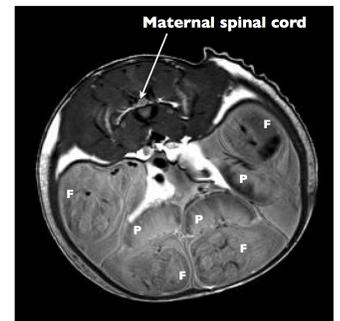


Figure 1: T₂-weighted image showing four fetuses at G20. Placentas (P) and fetuses (F) are identified. The delineation between the amniotic cavities (placenta and fetal organs) are clearly visible.

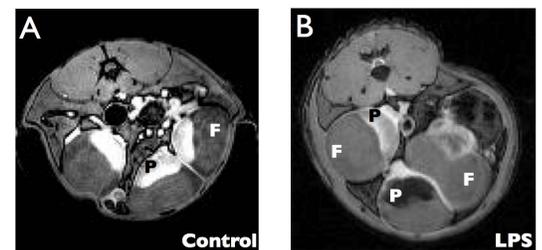


Figure 2: T₁-weighted images showing a control dam (A) and the corresponding placental hypointensities in and a LPS-treated dam (B).