Inflammatory and Iron-Related Indices Relate to Neonatal White Matter Microstructure

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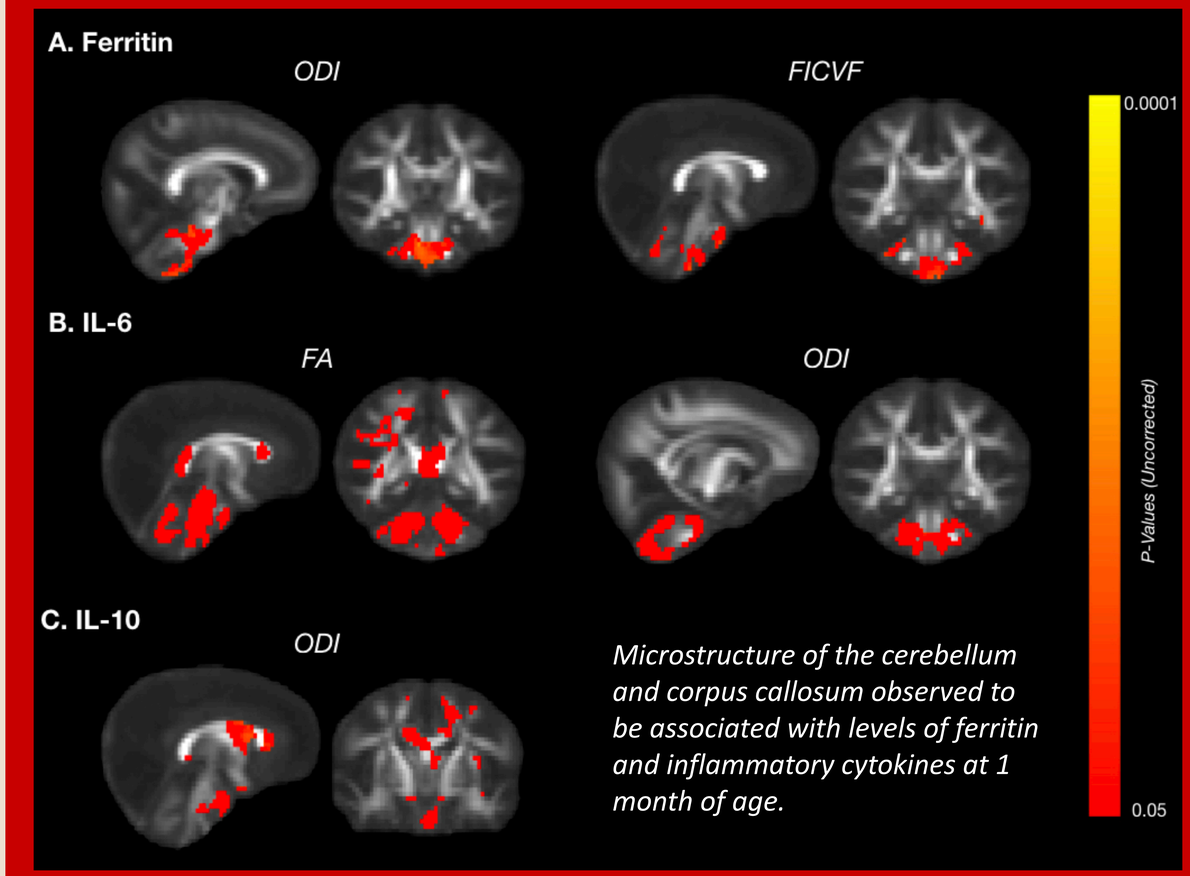
BACKGROUND

- Iron endowment is critical for healthy development, while iron deficiency at birth is linked to a proinflammatory propensity[1,2]
- White matter (WM), essential for brain connectivity, is sensitive to adverse environments, which can have long-lasting effects on development[3,4].
- However, molecular mechanisms underlying infant behavior and brain development are not understood.
- **Objective:** To examine associations between iron-mediated inflammatory pathways and WM microstructure in 1-month old infants.

METHODS

- Women enrolled during second trimester of pregnancy.
- Cord blood (CB) specimens collected at birth and plasma was separated by centrifugation on average 12 hours after collection.
- Assays of CB plasma performed to measure iron indices (e.g., ferritin and hepcidin) and cytokines (i.e., IL-6, IL-8, IL-10, tumor necrosis factor-α [TNF-α]).
- Multi-modal MRI was acquired at 1-month of age during non-sedated sleep.
  - Diffusion Tensor Imaging (DTI) and Neurite Orientation Dispersion and Density (NODDI) characterized WM microstructure[5].
- A total of 47 participants with both CB measures and DTI/NODDI data.
- *Statistical Analyses:*
  - Non-parametric permutation tests examined associations between iron/cytokine levels and DTI/NODDI measures
  - Measures controlled for corrected gestational age, sex, and head motion.

RESULTS



Microstructure of the cerebellum and corpus callosum observed to be associated with levels of ferritin and inflammatory cytokines at 1 month of age.

- Voxelwise analyses revealed correlations across early developing white matter regions.
- Figure 1 provides representative sagittal and coronal views of white matter correlations. Areas of red-yellow denote regions of marginal significance ($p<0.15$, FWE-corrected).
- Ferritin levels negatively associated with Orientation Dispersion Index (ODI; $p<0.05$, uncorrected; Fig. 1a) and the intracellular volume fraction (FICVF; $p<0.05$, uncorrected; Fig. 1A). Regions associated with ferritin included the cerebellum, pons, and brain stem.
- IL-6 was negatively related to indices of WM, including fractional anisotropy (FA), diffusivity, and orientation dispersion ($p<0.05$, uncorrected; Fig. 1B). Regions included cerebellar WM, brain stem and corpus callosum.
- Negative correlations between IL-10 and ODI were also observed in the body of the corpus callosum and brain stem ($p<0.05$, uncorrected; Fig. 1C).

CONCLUSIONS

- Findings link levels of CB inflammatory cytokines and iron stores at delivery to WM maturation in several brain regions including cerebellum and corpus callosum.
- Results did not survive correction for multiple comparisons, but potentially offer insights into associations between iron-mediated inflammatory pathways and WM development.
- Future analyses will test the strength of associations between cytokine and iron biology and WM maturation in a larger sample of infants.

ADDITIONAL KEY INFORMATION

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