The role of sex and inflammation on the developing brain in neonatal abstinence syndrome (NAS)

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Male infants exposed prenatally to opioids are more likely to develop withdrawal signs (NAS), require pharmacotherapy (NAS-Tx) and have longer hospitalizations compared to females. Emerging animal data show that opioids exert sex-dependent inflammatory effects through non-neuronal pathways. Opioid binding to TLR4 on glial cells stimulates inflammatory mediator release and brain injury, reinforcing reward/addictive behavior with deleterious effects on cognition. We aim to understand a potential sex-specific impact of prenatal opioid exposure on pro-inflammatory pathways and the developing brain using neonatal saliva and magnetic resonance imaging (MRI). Saliva samples were collected within 48 hours of birth from neonates with NAS (n=16) and non-opioid exposed infants (sex- and age-matched controls; n=16). Samples underwent transcriptomic analyses for pro-inflammatory (IL1B, IL6, TNFα, CXCL1, MCP1), anti-inflammatory (IL10), and key reward-signaling (DRD2) genes. Compared to controls, neonates with NAS had 3-fold higher expression of IL6 and MCP1, with even higher expression (5-fold) in NAS-Tx (p≤0.05). Females with NAS-Tx had 4-fold higher expression of IL1B, IL6, MCP1, and downregulation (<1-fold expression) of IL10 than males (p≤0.05); the expression of IL6 and MCP1 correlated with DRD2 (r=0.99, p<0.05). White matter hyperintensity was seen in four of five females with NAS, one male with NAS had a normal MRI. All controls had a normal MRI. Functional MRI is ongoing. Prenatal opioids may promote inflammation and reinforce reward properties, with a greater effect in females than in males. Whether inflammation contributes to the severity of NAS and white matter abnormalities in females remains subject to further research in larger cohorts.