Prenatal Chorioamnionitis Plus Early Postnatal Intraventricular Hemorrhage Models Post-hemorrhagic Hydrocephalus of Prematurity

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Introduction

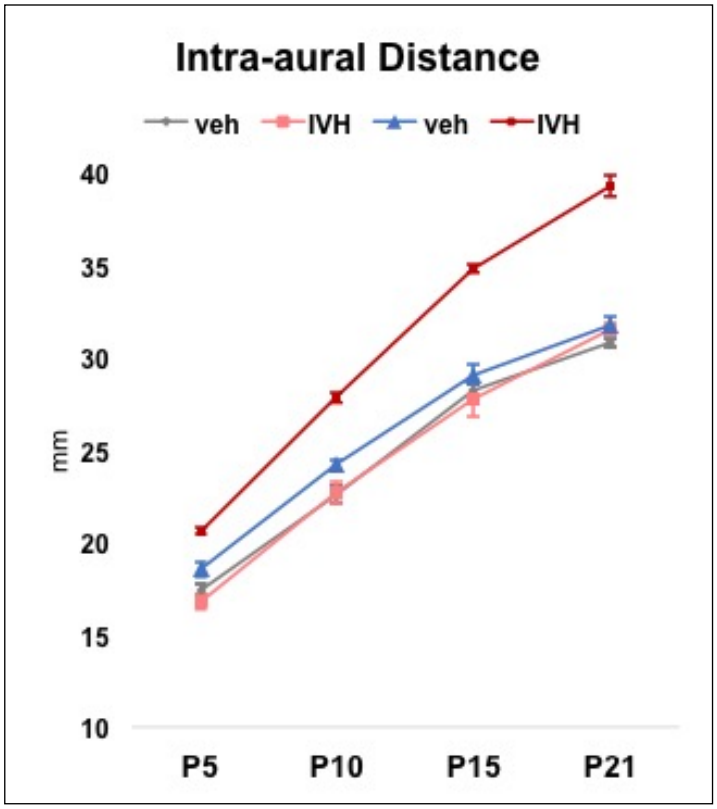
Chorioamnionitis is the main cause of spontaneous very preterm birth. Very preterm newborns are prone to intraventricular hemorrhage (IVH) and a subset of these newborns develops symptomatic post-hemorrhagic hydrocephalus (PHH). Few age-appropriate, translatable rodent models exist to study mechanisms of PHH. Our objective was to develop a rodent model of PHH to study the repair of ventricular CSF flow following chorioamnionitis plus IVH.

Methods

Chorioamnionitis was induced on embryonic day 18 (transient systemic hypoxia-ischemia plus intra-amniotic lipopolysaccharide). Rat pups were born at term (~30 weeks of human gestation). On postnatal day 1 (P1), lateral ventricles from pups of both sexes were injected with lysed red blood cells from a littermate. Intra-aural distance (surrogate for head circumference) was measured daily. Ventriculomegaly was quantified with MRI. Ependymal cells were assayed for markers of cilia function using qPCR, immunoblotting and immunohistochemistry. Groups were compared with two-way ANOVA and post-hoc correction, with $p<0.05$ significant.

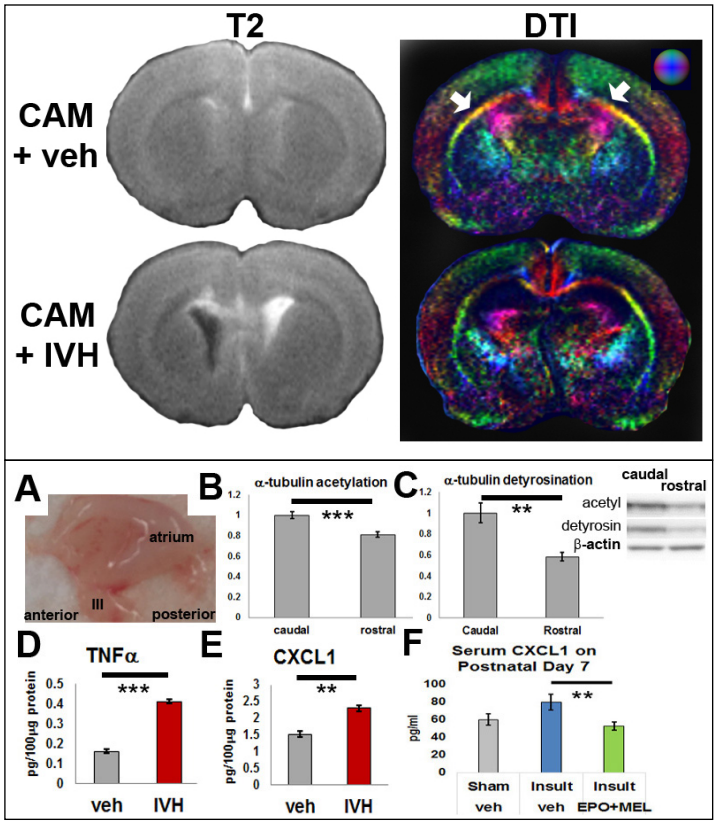
Learning Objectives

By the conclusion of this session, participants should be able to 1)describe the contribution of prenatal injury to the development of post-hemorrhagic hydrocephalus, 2) discuss how ependymal cilia injury disrupts CSF flow, 3) and recognize how interventions may restore CSF flow



Results

Rats with chorioamnionitis plus IVH developed progressive macrocephaly and ventriculomegaly, documented by MRI, while controls (sham-IVH, insult-veh) did not exhibit progressive macrocephaly or ventriculomegaly. Ex vivo MRI performed on P9 insult-veh and insult-IVH rats showed ventriculomegaly only after postnatal IVH. Initial analyses show that IVH increases ependymal inflammatory response on P2, with elevation of ependymal tumor necrosis factor-alpha (TNF-a, $p<0.001$) and CXC-chemokine-ligand 1 (CXCL1, $p<0.01$), compared to vehicle (n=3-5). Analysis of rostral and caudal P5 ependymal cultures revealed changes in alpha-tubulin acetylation and detyrosination, markers of ependymal cilia maturation.



Conclusions

Initial results suggest that PHH of prematurity results from the combination of early inflammatory insult from chorioamnionitis plus IVH and subsequent damage to ependymal motile cilia during a vulnerable developmental window. This clinically-relevant model may be useful to evaluate emerging neuro-reparative interventions. Insights from this work may extend to other etiologies of congenital hydrocephalus and reduce dependence on CSF shunts.

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