C-Section Prevents Cerebral Microhemorrhages in a Model of Encephalopathy of Prematurity

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CNS 2017 ANNUAL MEETING
BOSTON, MASSACHUSETTS
OCTOBER 7–11, 2017

Introduction

Encephalopathy of prematurity (EP) is a broad designation that encompasses the neurological pathologies that are common after preterm birth and are associated with neurological deficits in survivors. A common feature of EP is cerebral microhemorrhages. Here, we sought to understand the contributors to and consequences of cerebral microhemorrhages in the neonatal period and how mode of birth, vaginal or abdominal (Caesarian (C)-section), affected their incidence/severity. We report on a novel rat model of EP in which exposure to two pro-angiogenic stimuli in-utero predisposes to cerebral microhemorrhages during birth and are associated with long-term neurological deficit.

Methods

Pregnant Wistar rats were subjected to intrauterine ischemia (IUI) and maternal lipopolysaccharide (mLPS) at embryonic day (E) 19. Pups were born vaginally or abdominally at E21-22. Brains were evaluated for angiogenic markers (data not shown), microhemorrhages, myelination, and axonal development. Neurological function (social, motor, and cognitive behavior) was assessed until 6 weeks.

Results

Intrauterine ischemia and inflammation (IUI+mLPS) led to prominent hemorrhages, white matter damage, axonopathy, and behavioral deficits in injured pups after vaginal delivery. In pups exposed to the same

Results (cont.)

prenatal insults of IUI+mLPS but delivered via C-section, hemorrhages were minimal, neurological function was similar to controls, and myelination was better persevered.

Conclusions

Intrauterine pro-angiogenic stimuli (IUI+mLPS) predisposed to vascular fragility, led to cerebral microhemorrhages, and were associated with long-term white matter damage and neurodevelopmental deficit. These outcomes were avoided if injured pups were delivered via C-section.

Hemorrhage Size & Incidence

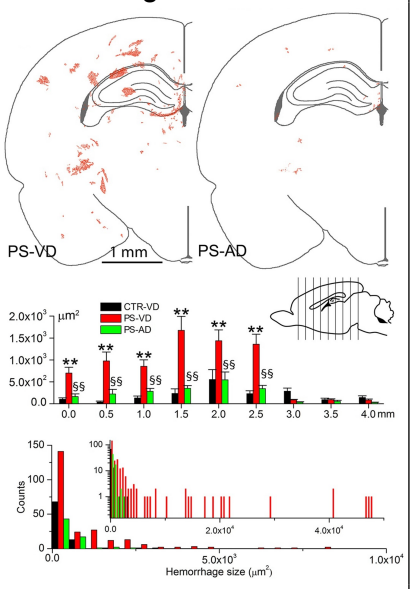

Fig. 1: Panel I: Maps showing locations & sizes of microbleeds identified in the coronal section 2.5 mm from the rostral extent of the lateral ventricle in P0 pups following IUI+mLPS and vaginal delivery (PS-VD) or abdominal delivery (PS-AD) Panel II: Averages of the total area occupied by hemorrhages in 9 coronal sections in CTR-VD pups, PS-VD pups, & in PS-AD pups. Panel III: Histogram showing the frequency distribution of microbleeds by size.

Neurodevelopmental Outcome

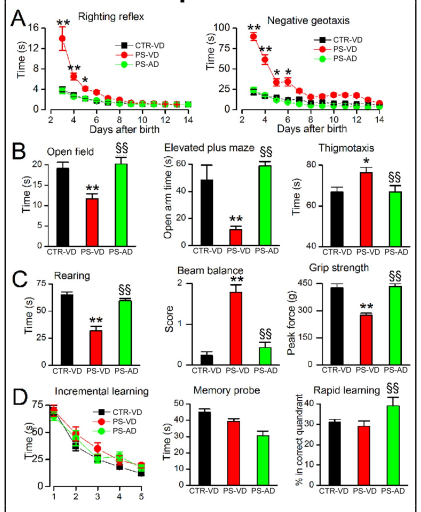

Fig. 2: A: Performance on early developmental behavioral tasks from P3–14 in CTR-VD, PS-VD, and PS-AD. B: Performance at 5 weeks on the open field test, the elevated plus maze, and on thigmotaxis. C: Spontaneous rearing, performance on the beam balance test, and grip strength at 5 weeks. D: Performance on the Morris water maze at 6 weeks.

References

Ballabh P et al. (2007) Angiogenic inhibition reduces germinal matrix hemorrhage. Nat Med 13: 477–485.
Segovia KN et al. (2008) Arrested oligodendrocyte lineage maturation in chronic perinatal white matter injury. Ann Neurol 63: 520–530.

White Matter Integrity

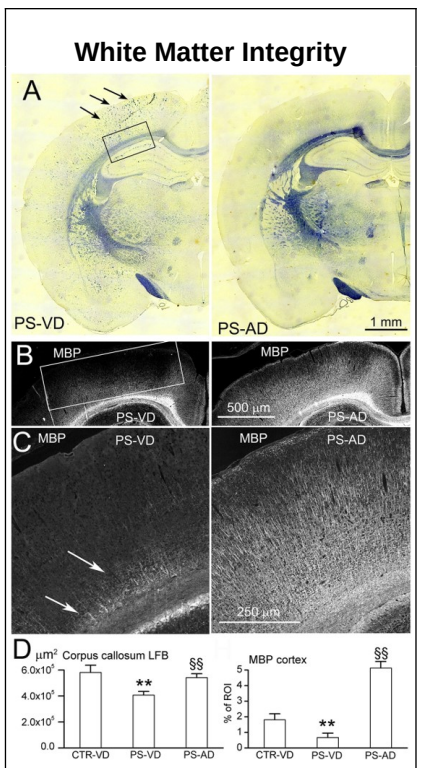

Fig. 3: A-C: Representative images of white matter staining (A) and MBP immunolabeling (B,C) at P52 in CTR-VD, PS-VD, PS-AD. Arrows in (A) point to clumped myelinated fibers; arrows in (C) point to poorly myelinated fibers above corpus callosum D: Quantification of staining and immunolabeling.