Angiogenesis Dysregulation in the Plasma of Term Asphyxiated Newborns Treated with Hypothermia

Henna Shaikh [1], Elodie Boudes [1], Zehra Khoja [1], Michael Shevell [2], Pia Wintermark [1]

(1) Division of Newborn Medicine; (2) Division of Pediatric Neurology; Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada

BACKGROUND

- Hypoxic-ischemic encephalopathy (HIE) due to birth asphyxia at term is a major cause of long-term neurological impairment, including cerebral palsy, mental retardation, and epilepsy.
- Mild hypothermia is the current standard treatment for HIE.
- This treatment is cumbersome, must be initiated within 6 hours of life and continued for 72 hours, and does not consistently prevent brain hypoxic-ischemic (HI) injury.
- More robust and versatile therapies are needed.
- Therapies targeting angiogenesis have shown improved outcomes following stroke in adults.
- Angiogenesis following birth asphyxia in term newborns has not been systematically studied and merits further investigation.

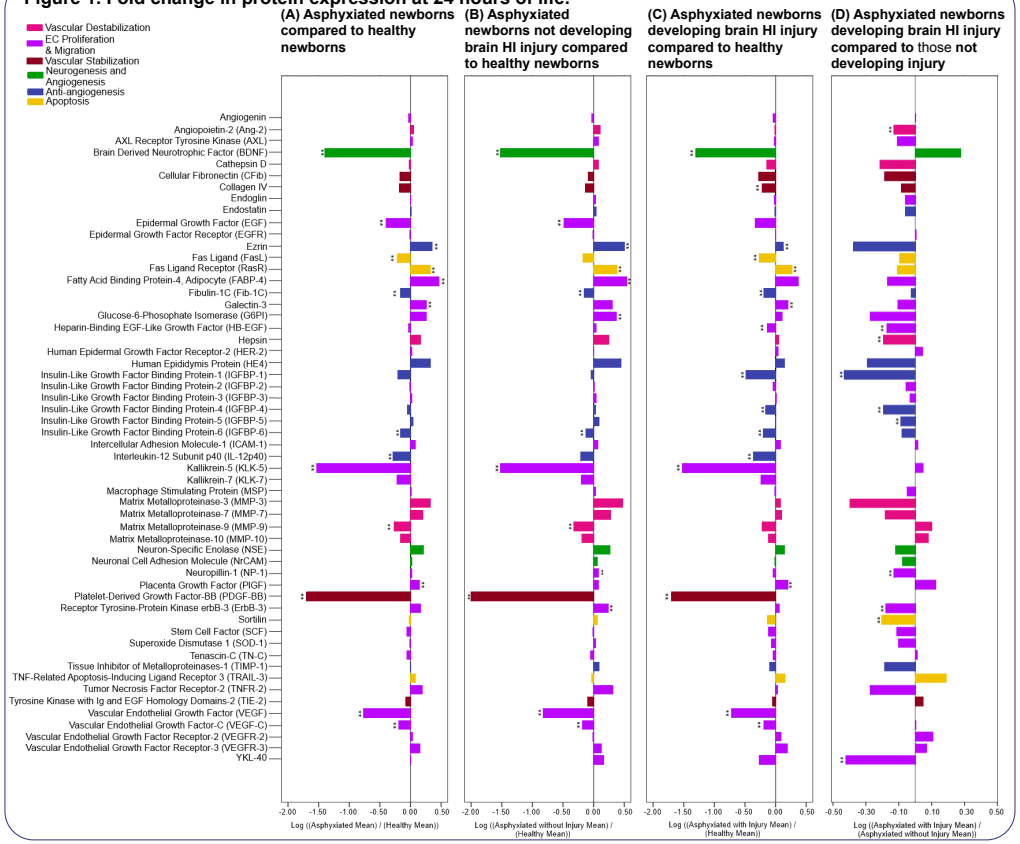
OBJECTIVE

- **To assess the expression of angiogenesis-related proteins in the plasma of term asphyxiated newborns who do and do not develop brain HI injury in comparison to healthy newborns.**

METHODS

- Prospective cohort study
- 12 term asphyxiated newborns meeting criteria for therapeutic hypothermia (gestational age ≥ 36 weeks and birth weight ≥ 1800 g; whole-body cooling to an esophageal temperature of 33.5ºC)
- Of the 12 asphyxiated newborns, 6 developed brain HI injury and 6 did not
- 4 healthy term newborns (controls)
- Plasma samples collected at 24 hours of life from all patients
- Immunoassay analysis (Myriad RBM®) performed to compare mean concentrations of 57 angiogenesis-related proteins between groups

Figure 1. Fold change in protein expression at 24 hours of life.



RESULTS

- Expression of angiogenesis-related proteins differed significantly between asphyxiated newborns developing and not developing brain HI injury in comparison to healthy newborns.
- Asphyxiated newborns not developing brain HI injury showed increased expression of pro-angiogenic proteins FABP-4, G6PI, NP-1, and ErbB-3 and decreased expression of anti-angiogenic proteins Fib-1C and IGFBP-6 compared to healthy newborns.
- Asphyxiated newborns developing brain HI injury showed up-regulation of only two pro-angiogenic proteins, Gal-3 and PlGF, but did show down-regulation of many anti-angiogenic proteins, including Fib-1C, IGFBP-1, IGFBP-4, IGFBP-6, and IL-12, compared to healthy newborns.
- Compared to asphyxiated newborns not developing brain HI injury, asphyxiated newborns developing injury showed lower expression of pro-angiogenic proteins Ang-2, HB-EGF, hepsin, NP-1, ErbB-3, and YKL-40 and lower expression of anti-angiogenic proteins IGFBP-1, IGFBP-4, and IGFBP-5.

CONCLUSIONS

- Unlike those who are protected from brain HI injury, asphyxiated newborns who develop injury may fail to up-regulate pro-angiogenic proteins and instead down-regulate anti-angiogenic proteins in an attempt to compensate.
- **Increased angiogenesis may be an important mechanism for preventing or repairing brain HI injury in asphyxiated newborns and should be further investigated as a potential therapeutic target.**

Pia Wintermark received research grant funding from NeuroDevNet NCE Cerebral Palsy Demonstration Project and FRSQ Clinical Research Scholar Career Award Junior .