

## Time Course of Diffusion Restriction in Neonates with Hypoxic Ischemic Encephalopathy Treated with Hypothermia

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**Introduction:** Hypoxic Ischemic Encephalopathy (HIE) is a common cause of injury and death in term newborns (1) that can lead to lifelong sequelae such as severe motor and/or cognitive deficits. A recent development in the treatment of such infants is the use of systemic hypothermia begun within six hours of injury, which has been shown to improve neurological outcomes (2). Brain MRI is a standard tool for diagnosis of brain injury in HIE. Given the ischemic nature of the injuries, diffusion weighted imaging (DWI) is critical not only for the diagnosis of the extent and severity of the hypoxic insult but also for the timing of the injury. The changes in diffusion imaging following injury are dynamic, with diffusion imaging showing the strongest contrast 2 days after injury and "pseudo-normalizing" after that (3). Knowledge of the time course of diffusion changes after neonatal HIE has been established. However, the impact of hypothermic therapy on the chronology of these diffusion changes on MRI is unknown. We have assessed the time course of diffusion changes in infants with HIE treated with hypothermia and compare this to previously documented changes in infants not treated with hypothermia.

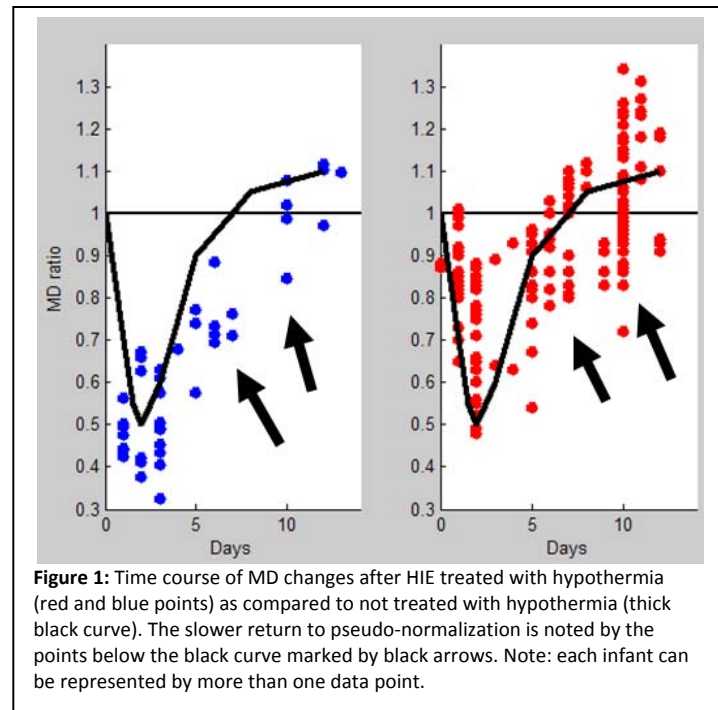
**Materials and Methods:** Retrospective review was performed on 66 neonates that underwent hypothermia treatment at our institute during the years 2007 to 2010. Eleven were excluded due to death, prematurity, and congenital anomalies. Average gestational age at birth was  $38.7 \pm 1.6$  wks and there were 29 males. Clinical MRI scans were performed on both 1.5T and 3T Siemens scanners (Erlangen, Germany) included anatomic imaging with T1- and T2-weighted images and DWI with calculated mean diffusivity (MD) values ( $b=1000$  s/mm<sup>2</sup>, 3-12 directions, variable resolution, with highest 2 mm<sup>3</sup>). There were 23 infants with 2 MRIs and 3 infants with 3 MRIs. Forty-Eight of the MRIs were performed between day 0 and 5; 40 were performed between day 6 and 15; 15 were performed after day 15. Anatomical scans were graded using a qualitative injury scale. Two complementary analyses of the MD were performed. In the first, 12 infants were identified with focal MD abnormalities on their first MRI scan (obtained at mean  $2.3 \pm 1.5$  days), and these areas were further measured on follow-up scans (obtained at mean  $9.0 \pm 1.5$  days) (blue dots in Fig.1). In order to compensate for sources of variability such as location in the brain and different scanners, a MD ratio was formed by dividing each MD by the normal MD value in the contralateral side of the brain. The second analysis followed closely the methods in (3). Sixteen neonates were identified with focal injury present after day 5, identified on either anatomic imaging or on DWI using the qualitative scoring. The MD in these areas was then measured longitudinally across all the scans available for that infant (red dots in Fig.1). The MD ratio in this case was formed by dividing the MD by an average MD obtained from 15 infants with HIE treated with hypothermia, but with normal brain MRI on qualitative evaluation. Two infants with global injury that subsequently died were excluded from both groups.

**Results:** The figure demonstrates the time course of focal diffusion abnormalities in our cohort analyzed using the two different approaches described above (in blue and red). The thick black curve approximates the MD time course in infants not treated with hypothermia as adapted from Fig. 1 in (3). Although there is overlap between the data from cooled and non-cooled infants, neonates treated with hypothermia demonstrate a slower recovery of the MD to the point of pseudo-normalization as compared to prior reports (black arrows), which may be as late as 10-12 days in neonates treated with hypothermia as compared to 5-7 days in prior studies without hypothermia treatment.

**Conclusions:** There are differences in the recovery time of restricted diffusion lesions in HIE neonates treated with hypothermia as compared to those not treated with hypothermia. These changes appear to extend the window in which HIE lesions are visible on DWI sequences and have implications for the radiologic interpretation of these studies.

### References:

1. Rutherford M. et al., *Lancet Neurology* 2010; 9:39-45.
2. Jacobs S. et al., *Cochrane Database of Systemic Reviews* 2007; Issue 4.
3. McKinstry R. et al., *Neurology* 2002; 59:824-833.



**Figure 1:** Time course of MD changes after HIE treated with hypothermia (red and blue points) as compared to not treated with hypothermia (thick black curve). The slower return to pseudo-normalization is noted by the points below the black curve marked by black arrows. Note: each infant can be represented by more than one data point.