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Clinical Observations

Therapeutic Hypothermia in Neonates and Selective Hippocampal Injury on Diffusion-Weighted Magnetic Resonance Imaging

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ABSTRACT

BACKGROUND: Hippocampal injury is most often observed in conjunction with basal ganglia injury after hypoxia-ischemia in term newborns. Objective was to determine perinatal characteristics leading to selective hippocampal injury vs basal ganglia injury on diffusion-weighted imaging in term encephalopathic infants following intrapartum hypoxia-ischemia treated with selective head cooling and to correlate specific injury to subsequent neurodevelopmental outcome. **METHODS:** Retrospective chart review of obstetric and/or perinatal risk factors and patient characteristics in term infants treated with selective head cooling. All infants met standard enrollment criteria for cooling. MRI was obtained at a median of 7 days of life. Abnormal outcome was defined as spastic quadriplegia, cognitive delay, both, or death. **RESULTS:** Fifty-seven infants were included for analysis. Diffusion-weighted imaging findings included normal (n = 31), basal ganglia injury (n = 16), and selective hippocampal injury (n = 10). No differences in gestational age, birth weight, sex, or labor complications between groups. More infants in the basal ganglia vs hippocampal group required delivery room cardiopulmonary resuscitation ($P = 0.05$), exhibited persistent severe acidosis, severe amplitude electroencephalography suppression, and encephalopathy at birth ($P < 0.05$). Abnormal neurodevelopmental outcome or death was observed in 88% vs 10% of infants in the basal ganglia vs the hippocampal group, respectively ($P = 0.0001$). **CONCLUSIONS:** Infants with hippocampal injury on diffusion-weighted imaging recovered from an intrapartum asphyxial insult more rapidly as reflected by an earlier correction of acid-base status, were less likely to need cardiopulmonary resuscitation, and were less severely encephalopathic. These findings highlight the exquisite vulnerability of the hippocampus to acute hypoxia unaffected by selective head cooling, whereas the normal appearance of the basal ganglia in these infants suggests a neuroprotective effect of cooling.

Keywords: cerebral hypoxia-ischemia, hippocampus, hypothermia, induced, infant, newborn

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Introduction

Hypoxic-ischemic changes in the term newborn identified on brain imaging have been described as reflecting a variety of patterns ranging from parasagittal injury; focal and multifocal cerebral injury; selective neuronal necrosis of the cerebral cortex, basal ganglia, thalamus, and hippocampus; and finally brain stem injury.[1] There may be significant overlap between these patterns as well. Although the hippocampus has been described as being particularly vulnerable to hypoxic-ischemic change, it is rare to observe isolated hippocampal injury without additional hypoxic-ischemic changes particularly within the basal ganglia (BG) on magnetic resonance imaging (MRI) imaging.[2-4]

Studies have demonstrated improved neurodevelopmental outcome in survivors treated with therapeutic hypothermia after perinatal hypoxia-ischemia.[5] For this reason, it is recommended that therapeutic hypothermia,

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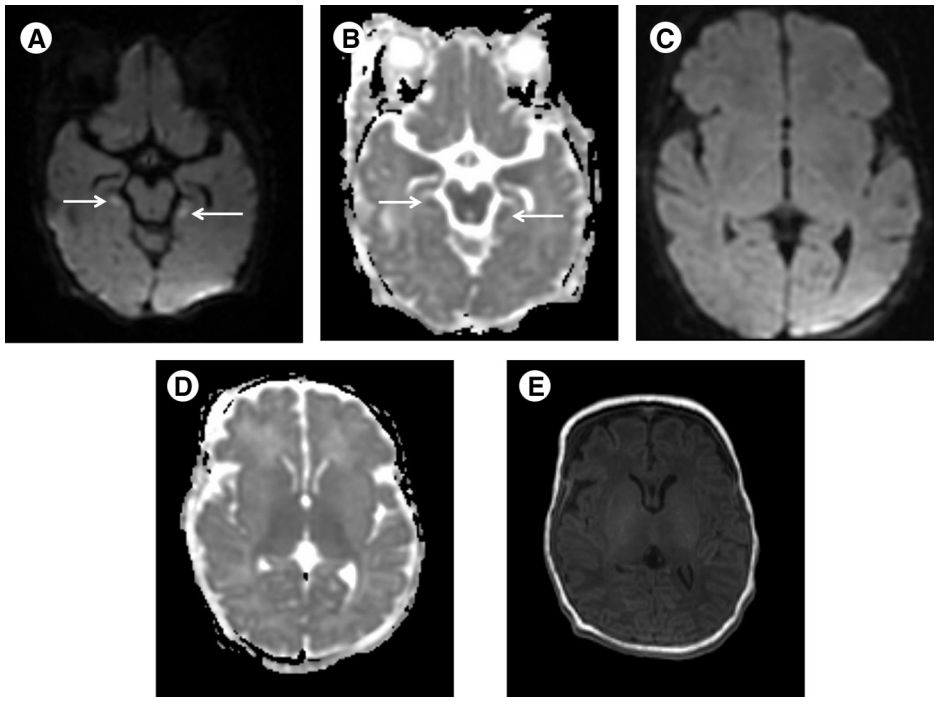

FIGURE.
Term infant delivered via emergent cesarean section for abnormal fetal heart rate tracing, Apgar scores 2, 5, and 6. Initial pH of 7.25 and base deficit of −10. Seizures were detected on amplitude-integrated electroencephalography at enrollment and Sarnat stage 2 encephalopathy on clinical examination. Selective head cooling initiated at 5.5 hours of life. Infant is developing normally at 14 months of age. Magnetic resonance imaging was obtained on day of life 8. Diffusion-weighted imaging image with high signal intensity within the hippocampi bilaterally (white arrows) (A). Apparent diffusion coefficient map showing restricted diffusion in the hippocampi bilaterally (white arrows) (B). Normal diffusion-weighted imaging at level of basal ganglia and thalamus (C). Normal apparent diffusion coefficient map at level of basal ganglia and thalamus (D). Normal T1-weighted image of basal ganglia and thalamus (E).

with either selective head cooling (SHC) or whole-body cooling, should be offered to all term or near-term infants with evolving moderate-to-severe hypoxic-ischemic encephalopathy (HIE).[6] There is now great interest in assessing the patterns and severity of injury evident on follow-up MRI of infants treated with therapeutic hypothermia.[7-11] We have treated term infants at risk for evolving HIE with SHC at our center and have identified a subset of infants with predominant hippocampal injury, without BG changes, on diffusion-weighted MRI (Fig). The aims of this study were (1) to determine perinatal characteristics leading to hippocampal vs BG injury in the setting of hypoxia-ischemia and (2) to correlate the predominant injury pattern to subsequent neurodevelopmental outcome.

Methods

Study population

The study population included both inborn and referred infants treated with SHC in the neonatal intensive care unit at Weill Cornell Medical Center, New York-Presbyterian Hospital, between May 2007 and June 2011. Weill Cornell Medical College Institutional Review Board approved this study. Infants were eligible for SHC if gestational age (GA) ≥36 weeks with at least one of the following: significant perinatal event during labor (i.e., fetal bradycardia); Apgar score ≤5 at 10 minutes; continued need for resuscitation including endotracheal intubation or bag-mask ventilation at 10 minutes; acidosis defined by cord arterial pH or any postnatal arterial pH <7.00 within 1 hour of life; or base deficit ≥16 mmol/L in an umbilical cord sample or any blood sample obtained within 1 hour of birth (arterial or venous). Infants also must demonstrate clinical evidence of Sarnat stage 2 or 3 encephalopathy and moderate and/or severe amplitude-integrated electroencephalography (aEEG) suppression with the exception of cases where artifact rendered the aEEG uninterpretable.[12] Severely encephalopathic infants without spontaneous activity or respirations and infants >6 hours of life were not eligible for treatment. SHC was initiated within 6 hours of life. All infants were cooled to goal rectal temperature of 34.5°C for 72 hours and were rewarmed >4-6 hours after this period per protocol.

Clinical characteristics

The infants' charts were retrospectively reviewed for the following characteristics: GA, birth weight (BW), sex, labor complications (i.e., placental abruption and uterine rupture), fetal heart rate tracing abnormality, meconium, mode of delivery (i.e., vaginal, routine or emergent cesarean section, and/or vacuum-assisted delivery), need for cardiopulmonary resuscitation (CPR) in the delivery room, 5- and 10-minute Apgar scores, arterial cord pH, and base deficit. Postnatal information collected included initial pH, base deficit, lactate, and bicarbonate levels. Amplitude electroencephalography was recorded with the Olympus CFM 6000 Infant aEEG Cerebral Function Monitor (Natus, San Carlos, CA). Amplitude electroencephalography was classified as previously described by al Naqeeb et al.,[13] with moderate suppression defined as the upper margin of band of aEEG activity >10 μV and the lower margin ≤5 μV; and severe suppression with the upper margin of the band of aEEG activity <10 μV and lower margin <5 μV. Presence of seizures at the time of enrollment was also noted, defined either by clinical findings and/or aEEG. Encephalopathy staging was classified based on clinical examination and characterized using modified Sarnat stages as follows: stage 1—hyperalert, exaggerated Moro, generalized sympathetic effects, and normal tone; stage 2—lethargy, hypotonia, strong distal flexion, weak or absent suck, and parasympathetic effects including bradycardia and miosis; and stage 3—stuporous, flaccid, suppression of brain stem, and autonomic function.[12]