Delayed Onset of Sleep-Wake Cycling with Favorable Outcome in Hypothermic-Treated Neonates with Encephalopathy

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Objective To determine whether hypothermia modulates acquisition of sleep-wake cycling in term neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE) and the relationship to outcome.

Study design Twenty-nine term infants with moderate to severe HIE treated with selective head cooling were evaluated. All were monitored with amplitude-integrated electroencephalography during and video electroencephalography immediately after hypothermia for ≥72 hours. Electroencephalograpic data were analyzed for background and sleep-wake cycling. Abnormal outcome included death or severe global neurodevelopmental disability ≥18 months.

Results Acquisition of sleep-wake cycling was noted in nine infants by 72 hours, in 13 by 96 hours, 19 by 120 hours, and 22 by 144 hours. Presence of sleep-wake cycling was associated with normal outcome, that is, 14 of 22 (64%), versus abnormal outcome, that is, none of seven without sleep-wake cycling (P = .006). The presence of sleep-wake cycling by 120 hours had a positive predictive value of 68% and negative predictive value of 90%. Magnetic resonance imaging abnormalities were related to onset of sleep-wake cycling.

Conclusions Although onset of sleep-wake cycling is markedly delayed in term neonates with moderate to severe HIE treated with hypothermia, approximately 65% with acquisition of cycling have a normal outcome. Sleep-wake cycling is an important additional tool for assessing recovery in term infants with moderate to severe HIE treated with hypothermia. *(J Pediatr 2011;159:232-7)*.

The prognostic value of conventional electroencephalogram (EEG) and more recently amplitude-integrated EEG (aEEG) in neonatal hypoxic-ischemic encephalopathy (HIE) for neurodevelopmental outcome has been well studied.[1-11] Early establishment of continuous background activity is a marker of a more favorable outcome, whereas persistent discontinuous background, burst suppression, or low-voltage patterns are associated with abnormal outcomes.[1-5,10] Moreover, seizure, either clinical or electrographic, is an additional poor prognostic indicator.[2,8] In term infants, distinct EEG patterns of wakefulness and active and quiet sleep states have a mean duration of cycling of 60 minutes, with a range of 30-70 minutes.[12] Although conventional EEG remains the gold standard for determining the ontogeny of sleep-wake cycling, the aEEG is also able to identify this development.[13] Generation of sleep-wake cycling involves many regions of the brain and reflects the integrity, maturity, and organization of the entire neuronal network. Sleep-wake cycling is defined by clinical and electrophysiological variables including EEG waveform patterns. These state-dependent patterns are the physiological representation of complex interactions among cortical, basal forebrain, thalamic, and hypothalamic neurons, all of which receive substantial input from the ascending arousal system.[14,15] It follows that both focal and diffuse injury as in the case of hypoxia-ischemia may have significant effects on this large network and therefore on state-dependent EEG changes.[16] Thus, Osredker et al,[17] using the aEEG, studied 171 term infants with HIE and showed a linear correlation between the onset of sleep-wake cycling, the severity of encephalopathy, and neurodevelopmental outcome. Importantly, the time of onset of sleep-wake cycling was found to have a predictive value for neurodevelopmental outcome, with an onset of sleep-wake cycling less than 36 hours being associated with a favorable outcome.

Recently, induced hypothermia has been shown to improve the outcome of infants with moderate to severe HIE.[18-20] Several studies have addressed the prognostic value of background activity with conventional EEG and aEEG in term infants with HIE treated with hypothermia.[21-23] One very recent study suggests that the delayed evolution of sleep-wake cycling to 36 hours with hypothermia as compared with 24 hours in normothermic infants was still associated with a favorable outcome.[21] We have used hypothermia to treat infants with early moderate to severe encephalopathy. As part of the management, we have used continuous EEG monitoring during and after rewarming of the infant to assess cortical function. We sought to determine the impact

aEEG	Amplitude-integrated electroencephalogram
HIE	Hypoxic-ischemic encephalopathy
MDI	Mental Developmental Index
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PPV	Positive predictive value
vEEG	Video electroencephalogram

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of hypothermia on the evolution of sleep-wake cycling in this patient population. The study objectives were to determine (1) whether hypothermia modulates the onset of sleep-wake cycling; and (2) whether there is a relationship between the onset of sleep-wake cycling and subsequent neurodevelopmental outcome.

Methods

From June 2006 to October 2008, 31 consecutive neonates with moderate to severe HIE were treated with selective head cooling using the Cool-Cap System (Natus Medical Inc, San Carlos, California). We used specific enrollment criteria as determined by clinical examination and a cerebral function monitor (CFM6000 system; Natus Medical Inc). The monitor provides an aEEG as well as a single-channel, raw EEG tracing. Electrodes were placed over the frontotemporal regions for assessment before hypothermia and maintained in place for the duration of the hypothermia. This anatomic location was selected to maintain continuous monitoring during hypothermia.[16] All the infants were born at or transported to the neonatal intensive care unit at New York-Presbyterian Hospital for therapeutic hypothermia within 6 hours of life. The enrollment criteria included an Apgar score of 5 or less at 10 minutes after birth; a continued need for resuscitation including endotracheal or mask ventilation at 10 minutes after birth; or severe acidosis defined as pH less than 7.00 or a base deficit of 16 mmol/L or more in an umbilical cord blood sample or from an arterial or venous blood sample obtained within 60 minutes of life.[19] Eligible infants were assessed by one neonatologist (J.P.) for evidence of moderate or severe encephalopathy according to Sarnat staging.[27] The aEEG assessment of encephalopathy at the time of enrollment was either moderately abnormal, defined as upper margin >10 μV and lower margin <5 μV or severely abnormal, defined as upper margin less than 10 μV.[19,28] The infant's core temperature was maintained at 34.5°C for 72 hours. Anti-epileptic medications were administered for suspected clinical and/or electrographic seizures as follows.[29] Phenobarbital was the initial drug, followed by fosphenytoin, and a midazolam infusion was used to treat continuous electrographic seizure activity.[16] After assessment at enrollment, the aEEG was maintained during the 72 hours of hypothermia and was continued after cooling for 3 to 5 days. All infants were monitored with a XLTEK 32-channel computerized vEEG system (Natus Medical Inc), with standard 10-20 system montage with reduced number of electrodes (FP1, FP2, C3, C4, T3, T4, O1, O2, Fz, Cz), as well as the electrocardiogram for neonatal monitoring. The vEEG monitoring was started immediately after selective head cooling and maintained for at least 72 hours. The aEEG and conventional EEG are comparable when assessing background activity.[30,31] Magnetic resonance imaging (MRI) of the brain was performed at 7 days of age[32] with a GE Signa Genesis 3.0-T unit (GE Healthcare, Buckinghamshire, United Kingdom) with a regular head coil for the first five infants. Either a GE HDx 1.5- or 3.0-T unit with an eight-channel regular head coil or knee coil was used for the remaining infants. Some of the infants included in this study were part of a prior report.[16]

All infants were examined by a neonatologist (J.P.) and a pediatric neurologist (M.E.) at 3, 6, 9, 12, and 18 months of age. A developmental psychologist (G.R.) evaluated each infant's cognitive and language functions by using the Bayley Scales of Infant and Toddler Development, Third Edition. All evaluations were performed blinded to the onset of sleep-wake cycling. Normal outcome was defined as Mental Development Index (MDI) ≥85 and ambulation without difficulty or support. An abnormal outcome was defined as either death or severe disability, that is, MDI ≤70 or severe motor deficit restricting movement. Intermediate outcome was defined as a MDI >70 with or without a motor deficit.

The medical records were reviewed for the following characteristics: gestational age, birth weight, mode of delivery, Apgar scores, need for cardiopulmonary resuscitation in the delivery room, umbilical cord arterial pH, postnatal pH and base deficit, use of anti-epileptic medications, aEEG assessment at enrollment, and clinical evaluation at initiation of hypothermia including Sarnat staging and at follow-up.

EEG data were retrospectively analyzed by blinded reviewers (E.R. and V.Y.) for the following: background, epileptiform activity, and sleep-wake cycling. Sleep-wake cycling was defined as the presence of features of both wakefulness or active sleep and quiet sleep with at least two clear state changes during a 6-hour epoch (**Figures 1** and **2**).[12] In the term newborn, the mean duration of cycling is 60 minutes.[12] For the cumulative analysis of sleep-wake cycling, we assumed that sleep-wake cycling did not disappear once acquired.

Brain MRI was classified as follows: normal: no brain parenchymal lesions; mild: punctuate lesions of restricted diffusion, or subtle cortical T1 change; moderate: signal changes in diffusion weighted images, or T1-weighted images predominantly in the basal ganglia and/or thalami; and severe: extensive supratentorial restricted diffusion.

The Student *t* test (two-sided) and Fisher exact test were used where appropriate. All the values are mean ± standard deviation unless specified. Predictive values and receiver operator characteristic curves were calculated at each time period, that is, 72, 96, 120, and 144 hours. The Institutional Review Board of Weill Cornell Medical College approved the research.

Results

During the study period, 31 infants of birth weight 3265 ± 655 g and gestational age 39 ± 1.5 weeks met inclusion criteria. Of the 31 infants, 29 were evaluated and two infants (6.5%) were lost to follow-up. All 29 infants were evaluated at 18 months or older. Two infants were not testable because of the severity of impairment. The mean age at last follow-up evaluation was 22 ± 4.3 months.

Fourteen infants (48%) were normal. No infant had an intermediate outcome. Six infants had an MDI ≤70 and severe motor deficit restricting movement, indicating profound