Perinatal Acidosis and Hypoxic-Ischemic Encephalopathy in Preterm Infants of 33 to 35 Weeks' Gestation

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Objectives To determine the frequency of hypoxic-ischemic encephalopathy (HIE) in preterm infants of 33 to 35 weeks' gestational age on the basis of physiological screening for perinatal acidosis and neurological assessment of encephalopathy and to correlate neurodevelopmental outcomes with brain magnetic resonance imaging findings.

Study design This retrospective cohort study included all inborn infants of 33 to 35 weeks' gestation admitted to the neonatal intensive care unit at Parkland Memorial Hospital with perinatal acidosis from October 2005 to September 2008. Their medical records were reviewed, and pertinent data were recorded.

Results Of 1305 newborns, 2.5% (n = 33) had perinatal acidosis, and 27% (n = 9) of these had HIE (2, mild; 4, moderate; 3, severe). Persistence of metabolic acidosis on the first arterial blood gas obtained in the first hour of age was significantly associated with HIE ($P < .005$). Magnetic resonance imaging results were abnormal in 3 of 4 infants with moderate HIE and in both survivors with severe HIE. Death or disability occurred in no infants with mild or moderate HIE, but in all infants with severe HIE.

Conclusion Screening criteria for HIE that use biochemical and neurological assessments as performed in term newborns can be applied to preterm infants of 33 to 35 weeks' gestation. *(J Pediatr 2012;160:388-94)*.

Perinatal hypoxic-ischemic encephalopathy (HIE) remains a major cause of neurodevelopmental impairment. The diagnosis of HIE in full-term infants is made with well-defined and widely accepted criteria involving a step-wise combination of biochemical screening for perinatal acidosis and a standardized neurological examination for moderate-to-severe encephalopathy.[1,2] Newborns who are ≥36 weeks' gestation and have a diagnosis of moderate-to-severe HIE within the first 6 hours of age are selected for hypothermia therapy, which has improved neurodevelopmental outcomes and lessened the severity and extent of cerebral injury on magnetic resonance imaging (MRI).[1,3] In preterm infants, however, the diagnosis of HIE remains problematic, and these newborns have been excluded from hypothermia therapy because of insufficient evidence for safety or efficacy. Moreover, it is not known whether the screening criteria used to identify term asphyxiated newborns for cooling are appropriate for preterm infants.

Brain MRI is considered to be the best surrogate marker of cerebral injury and predictor of long-term neurodevelopmental outcome in term infants with HIE.[4] In term infants, the two major MRI patterns of brain injury are the "basal nuclei" predominant pattern following acute profound asphyxia and the "watershed" predominant pattern following partial prolonged asphyxia.[5-7] It remains unclear how these or other MRI findings apply to the asphyxiated preterm infant.

Therefore, the objectives of this study are to: (1) determine the frequency of HIE on the basis of physiological screening for perinatal acidosis and neurological assessment of encephalopathy in preterm infants of 33 to 35 weeks' gestational age; and (2) characterize the brain MRI findings in these preterm infants with clinical and laboratory evidence of HIE and correlate them with neurological outcomes after discharge from the hospital.

Methods

This retrospective cohort study included all inborn infants of 33 to 35 weeks' gestation who were admitted to the neonatal intensive care unit (NICU) at Parkland Memorial Hospital (PMH) with perinatal acidosis from October 2005 to September 2008. These infants were identified by review of a prospective neonatal database and

BSID	Bayley scales of infant development
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
PLIC	Posterior limb of internal capsule
PMH	Parkland Memorial Hospital
PVWM	Periventricular white matter

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L.C. is supported by the National Center for Research Resources (grants KL2RR024983 and UL1 RR024982). The authors declare no conflicts of interest.

Presented in part at the Pediatric Academic Societies' Meeting, May 5 to 8, 2007, Toronto, Canada (abstract 751111).

 10.1016/j.jpeds.2011.09.001

resuscitation registry[8] and included all admissions to the PMH NICU with perinatal acidosis. Umbilical cord arterial blood was routinely sampled on all deliveries at PMH from double-clamped sections of umbilical cord.[9] The infants' medical records were reviewed, and pertinent demographic, clinical, laboratory, and neuroimaging data were recorded. Gestational age assessment was based on the best obstetrical estimate with the date of the last menstrual period and ultrasonography, when performed, and then confirmed with a Ballard examination performed on admission to the NICU. Newborns who were not resuscitated or had lethal anomalies or other causes of encephalopathy not related to HIE were excluded. The study was approved by the institutional review board of the University of Texas Southwestern Medical Center.

Biochemical Screening for Perinatal Acidosis

Newborns with perinatal acidosis were identified with the same criteria used to screen for HIE in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network study of whole body hypothermia.[1] Specifically, these criteria consisted of: (1) A pH ≤7.0 or a base deficit ≥16 mEq/L on umbilical cord blood or any postnatal blood sample within 1 hour of age; or (2) history of an acute perinatal event and either no blood gas available, or a pH from 7.01 to 7.15 or a base deficit from 10 to 15.9 mEq/L, with a 10-minute Apgar score ≤5, or assisted ventilation initiated at birth and continued for at least 10 minutes.

Neurologic Assessment

The medical records of newborns with perinatal acidosis were reviewed for details of the neurological examination for HIE that was performed by the attending neonatologist within 24 hours of birth. Specifically, the results of the physical examination were reviewed for: (1) level of consciousness; (2) spontaneous activity; (3) posture; (4) tone; (5) primitive reflexes; and (6) autonomic nervous system signs, as described in the NICHD Neonatal Research Network study of whole body hypothermia.[1] Infants were categorized as having mild (stage I), moderate (stage II), or severe (stage III) HIE with the modified Sarnat staging for HIE.[1]

Magnetic Resonance Imaging

Imaging was done at >1 week of age by using T1 and T2 images, T2 gradient echo, and diffusion-weighted imaging. Two experienced pediatric neuroradiologists who were blinded to the infant's gestational age and clinical status reviewed the MRI studies. Images were assessed for presence and severity of pathologic T1 shortening and T2 prolongation, restricted diffusion, intracranial/intraventricular hemorrhage and periventricular leukomalacia. MRI findings were further graded according to published criteria in term newborns: grade 0, normal; grade 1a, minimal cerebral abnormality without involvement of the basal ganglia or of the posterior limb of the internal capsule (PLIC); grade 1b, more extensive cerebral involvement, but no involvement of the basal ganglia or PLIC; grade 2a, basal ganglia or PLIC abnormalities, but no cerebral abnormalities; grade 2b, both basal ganglia and PLIC involvement; and grade 3, hemispheric devastation.[5,6]

Neurodevelopmental Assessment

Infants in whom HIE was diagnosed were seen at the Follow-up Clinic at Children's Medical Center Dallas as per standard practice. When available, information on psychometric testing performed by a certified psychometrician with the Bayley Scales of Infant Development III (BSID; mean ± SD score, 100 ± 15) was obtained. Severe disability was defined by a BSID III score >2 SD less than the mean (ie, <70). Moderate disability was defined as a BSID III score between 1 and 2 SD less than the mean (ie, 85-70).

Statistical Analysis

Data analysis was performed with Sigma Stat software version 11.0 (SPSS, Chicago, Illinois), with results reported as the mean ± SD or as the number and percentage. Nonparametric analyses were used when indicated to compare clinical and laboratory variables in infants with and without HIE. A paired *t* test was used to compare umbilical cord blood gas and the first arterial blood gas parameters for each patient. Two-tailed tests were considered significant when the *P* value was ≤.05.

Results

In 1305 newborns admitted to the PMH NICU at 33 to 35 weeks' gestation, biochemical screening was performed on umbilical cord blood (n = 1275) or a blood sample obtained within 1 hour of birth (n = 30). Thirty-three newborns (2.5%) were identified with perinatal acidosis that was detected in 32 of the infants with umbilical cord blood sampling. In one newborn, acidosis was detected on the first arterial blood gas within 1 hour of age (**Figure**; **Table I**). Overall, 22 of those 33 newborns (67%) met the first biochemical screening criterion, and 11 met the second one. Most mothers of newborns with perinatal acidosis were of Latino/Hispanic ethnicity (n = 26; 79%), 4 (12%) were black, and 3 (9%) were Caucasian. These percentages were similar to the ethnicity and race of the delivery population at PMH. Mode of delivery was cesarean delivery in 25 newborns (78%) and vaginal delivery in 8 newborns (22%). Pregnancy was complicated by hypertension in 12 newborns (36%), diabetes mellitus in 6 newborns (18%), and placental abruption in 3 newborns (9%). Blood cultures from all 33 newborns on admission to the NICU were sterile, and no infant had a lumbar puncture.

Neurologic Assessment

Clinical signs of encephalopathy were documented in 9 of the 33 newborns (28%) with perinatal acidosis (**Figure**). These newborns did not differ significantly from newborns without HIE in birth weight, gestational age, sex, Apgar scores, need for resuscitation at birth, and umbilical cord