Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury

Hannah C. Glass, MDCM, David Glidden, PhD, Rita J. Jeremy, PhD, A. James Barkovich, MD, Donna M. Ferriero, MD, and Steven P. Miller, MDCM

Objective To examine whether neonatal seizures are associated with neurodevelopmental outcomes in infants with hypoxia-ischemia independent of the presence and severity of brain injury seen on magnetic resonance imaging (MRI).

Study design We used multivariate regression to examine the independent effect of clinical neonatal seizures and their treatment on neurodevelopment in 77 term newborns at risk for hypoxic-ischemic brain injury. Clinical seizures were recorded prospectively, and high-resolution newborn MRI measured the severity of brain injury. The outcome measure was the Full-Scale Intelligence Quotient (FSIQ) of the Wechsler Preschool and Primary Scale of Intelligence-Revised and neuromotor score at age 4 years.

Results After controlling for severity of injury on MRI, the children with neonatal seizures had worse motor and cognitive outcomes compared with those without seizures. The magnitude of effect varied with seizure severity; children with severe seizures had a lower FSIQ than those with mild/moderate seizures ($P < .0001$).

Conclusions Clinical neonatal seizures in the setting of birth asphyxia are associated with worse neurodevelopmental outcome, independent of the severity of hypoxic-ischemic brain injury. Randomized controlled trials are needed to determine whether differences in seizure treatment can improve outcome. *(J Pediatr 2009;155:318-23)*.

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Seizures in the newborn frequently signal an underlying brain disorder, such as hypoxic-ischemic injury, stroke, intracranial infection, or hypoglycemia.[1,2] Neonates with seizures are at high risk for mortality, and survivors commonly have adverse neurodevelopmental outcomes.[3-6] Do seizures themselves damage the developing brain, or are they merely a sign of the underlying brain disorder? This is an important and controversial question for neonatal medicine and neurology alike. Clinical management of neonatal seizures has remained unchanged for more than a generation, despite almost 10 years of evidence that phenobarbital—the most commonly used first line antiseizure agent in newborns—has limited efficacy[7] and is potentially neurotoxic in animal models.[8] Insight into whether seizures cause injury to the immature human brain has important implications for guiding clinical care and for determining appropriate outcome measures for clinical trials of antiseizure therapy in the newborn.

Accumulating animal evidence indicates that seizures in the neonatal period can alter brain development and lead to long-term deficits in learning, memory, and behavior.[9-11] In humans, there is no good evidence that seizures themselves affect neurodevelopmental outcome, however 2 studies using proton and phosphorous magnetic resonance spectroscopy suggest that seizure severity in infants with perinatal asphyxia is associated with brain injury and impaired metabolism independent of the severity of hypoxic-ischemic brain injury.[12,13]

The overlapping adverse effects of hypoxic-ischemic brain injury and early postinjury seizures have hindered determination of the independent neurodevelopmental consequences of neonatal seizures in humans. In the present study, we used a prospective cohort of term infants at risk for hypoxic-ischemic brain damage studied with high-resolution magnetic resonance imaging (MRI), a sensitive measure of the severity of hypoxic-ischemic brain injury in newborns, to assess the independent association between clinical seizures in the newborn period

CI	Confidence interval
EEG	Electroencephalography
FSIQ	Full-Scale Intelligence Quotient
MRI	Magnetic resonance imaging
SD	Standard deviation
SE	Spin-echo
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised

From the Departments of Neurology (H.G., A.J.B., D.F S.M.), Pediatrics (H.G., R.J., A.J.B., D.F.), Epidemiology & Biostatistics (D.G.), and Radiology (A.J.B.), University of California San Francisco, San Francisco, CA and Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada (S.M.)

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treated in accordance with local standards of care and long-term neurodevelopmental outcome.

Methods

Infants were eligible for inclusion if they were ≥ 36 weeks gestational age at birth and had any one of the following: umbilical cord artery or first blood gas pH < 7.1, umbilical cord artery or first blood gas base deficit >10, or 5-minute Apgar score ≤ 5. These broad inclusion criteria were chosen to encompass newborns with a wide range of injuries and neurodevelopmental outcomes and have been used in previous reports by our group.[6,12,14-18] Infants with suspected or confirmed congenital malformation, inborn error of metabolism, or congenital infection were excluded. The University of California San Francisco's Committee on Human Research approved the study protocol. An infant was studied only after informed voluntary parental consent was obtained.

Clinical Data

Trained neonatal research nurses prospectively extracted clinical data from maternal and infant records. The severity of encephalopathy was evaluated daily over the first 3 days using the Encephalopathy Score, which ranges from 0 to 6 and is based on physician assessment of alertness, feeding, tone, respiratory status, reflexes, and clinical seizures.[6]

Each newborn was prospectively assigned a composite seizure score using a chart review of nursing and physician progress notes and neurophysiology and hospital discharge summaries. This score, developed before study commencement, is heavily weighted toward *clinical* detection of seizures, reflecting the standard of care at the time of enrollment and the data available for this study. The total score ranges from 0 to 10 and includes scores for seizure frequency (1 point for more than 1 seizure, 2 points for status epilepticus), timing of onset (1 point for onset < 24 hours of life), anticonvulsant therapy (1 point for 1 or 2 medications, 2 points for ≥ 3 medications, 3 points for barbiturate coma), and neonatal electroencephalography (EEG) abnormalities (1 point for abnormal background without epileptiform discharges, 2 points for abnormal background with epileptiform discharges, 3 points for electrographic seizures, and 4 points for status epilepticus).[12] Here status epilepticus is defined as continuous seizures or multiple seizures without return to normal level of consciousness lasting longer than 20 minutes. EEG background is included in the score because of its known relationship to seizure risk.[19] At the time of hospital discharge, the total score was determined by adding together the highest score in each category. Because seizures are most severe early in the course of hypoxic-ischemic brain injury, the score is not affected by the duration of the patient's hospital admission. At the time of study enrollment, our center did not perform routine prolonged continuous video EEG or amplitude-integrated EEG. The composite seizure scores were subdivided into 3 seizure severity categories (0, no seizures; 1 to 3, mild/moderate seizures; and ≥ 4, severe seizures).

The infants were treated according to local standard of care, with phenobarbital as the first-line agent and phenytoin or lorazepam as add-on agents as needed. The children in this cohort were studied prior to implementation of therapeutic hypothermia at our center.

Magnetic Resonance Imaging

MRI was performed at a mean (± standard deviation [SD]) of 5.4 ± 3.0 days using a specialized neonatal head coil on a 1.5-Tesla Signa EchoSpeed system (GE Medical Systems, Milwaukee, Wisconsin). Imaging sequences were optimized for the neonatal brain and included 4-mm (1-mm "gap") sagittal spin-echo (SE) images (500/11/2 [TR/TE/excitations]), 4-mm (1-mm gap) axial SE images (500/11/2), and 4-mm (2-mm gap) axial SE images (3000/60,120/1) through the entire brain. The timing of imaging did not differ between the seizure groups ($P = .2$).

Severity of brain injury was measured using conventional T1-weighted (short-echo) and T2-weighted (long-echo) MRI. Previous work has demonstrated that this provides accurate measurements of brain injury for this age group. Diffusion-weighted imaging was not available during the early part of the study period and thus was not used for this analysis. A pediatric neuroradiologist who was blinded to the clinical history prospectively evaluated the MRI images. Injury to the basal nuclei and the watershed areas was scored independently using a system that is strongly predictive of neurodevelopmental outcome after neonatal encephalopathy.[14] The severity of the basal nuclei pattern of injury, which primarily evaluates deep gray matter and motor pathway injury, was scored as follows: 0, normal or isolated cortical infarct; 1, abnormal signal in the thalamus; 2, abnormal signal in the thalamus and lentiform nucleus; 3, abnormal signal in the thalamus, lentiform nucleus, and perirolandic cortex; or 4, more extensive involvement. The severity of the watershed pattern injury, which evaluates cortical and white matter injury, was scored as 0, normal; 1, single focal abnormality; 2, abnormal signal in anterior or posterior watershed white matter; 3, abnormal signal in anterior or posterior watershed cortex and white matter; 4, abnormal signal in both anterior and posterior watershed zones; or 5, more extensive cortical involvement. The pattern of injury was described as "basal nuclei–predominant," "watershed-predominant," or "normal."[16]

Neurodevelopmental Follow-Up

A developmental psychologist with experience in examining children with developmental impairment and who was blinded to the neonatal course examined the children at age 4 years using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R).[20] The WPPSI-R provides a full-scale intelligence quotient (FSIQ) with a mean of 100 (SD ± 15), as well as domain scores for Verbal and Performance IQs.

The 5-point neuromotor score was assigned by a neurologist (also blinded to the neonatal course), as described in our previous studies.[17] Children with a score ≥ 2 have an abnormal neuromotor examination, and those with a score ≥ 3 have a functional deficit (eg, cerebral palsy).