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

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Abstract

Objective—To determine whether neonatal seizures are associated with neurodevelopmental outcome in infants with hypoxia-ischemia, independent of the presence and severity of brain injury 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 was used to measure the severity of brain injury. The outcome measure was full-scale intelligence quotient (FSIQ) of the Wechsler Preschool and Primary Scale of Intelligence-Revised and the neuromotor score at four years.

Results—After controlling for severity of injury on MRI, children with neonatal seizures had worse motor and cognitive outcomes than 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 ($P < 0.0001$).

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 essential to determine whether differences in seizure treatment can improve outcome.

Keywords

Hypoxia-ischemia; brain Infant; newborn; Seizures; Magnetic resonance imaging; Intelligence tests

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INTRODUCTION

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 adverse neurodevelopmental outcome is common in survivors(3-6). Do seizures themselves damage the developing brain? Or, are they merely a sign of the underlying brain disorder? These are important and controversial questions for neonatal medicine and neurology alike. Clinical management for neonatal seizures has remained unchanged for more than a generation, in spite of almost ten years of evidence that phenobarbital - the most commonly used first line anti-seizure agent in newborns – has limited efficacy(7) and is potentially neurotoxic in animal models(8). Understanding whether seizures cause injury to the immature human brain has important implications for guiding clinical care and for informing appropriate outcome measures for clinical trials of anti-seizure therapy in the newborn.

There is accumulating animal evidence that seizures in the neonatal period can alter brain development and lead to long-term deficits in learning, memory and behavior(9-11). No good evidence has shown that seizures in humans affect neurodevelopmental outcome, although two 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 post-injury seizures have made it difficult to determine the independent neurodevelopmental consequence of neonatal seizures in human infants. We used a prospective cohort of term infants at risk for hypoxic-ischemic brain damage who were 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 treated according to local standard 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: (1) umbilical artery or first gas pH <7.1, (2) umbilical artery or first gas base deficit >10, or (3) 5-minute Apgar score ≤5. These broad inclusion criteria were chosen to encompass newborns with a wide range of injury and neurodevelopmental outcome and have been used in previous publications by our group(6,12,14-18). Infants were excluded if there was suspected or confirmed congenital malformation, inborn error of metabolism or congenital infection. The Committee on Human Research at the University of California, San Francisco, approved the protocol. Infants were studied only after informed voluntary parental consent.

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 three days using the Encephalopathy Score, which ranges from 0-6 and is based on physician assessment of alertness, feeding, tone, respiratory status, reflexes and clinical seizures(6).

Newborns were prospectively assigned a composite seizure score using chart review of nursing and physician progress notes, neurophysiology and hospital discharge summary. The score was developed prior to the study and is heavily weighted toward *clinical* detection

of seizures, which reflects the standard of care at the time of enrollment and the data available for this study. The score ranges from 0-10 and measures the seizure frequency (one point for >1 seizure, two for status epilepticus), timing of onset (one point for onset <24 hours of life), anticonvulsant therapy (one point for 1-2 medications, two for ≥3 medications, three for barbiturate coma), as well as the presence of neonatal electroencephalogram (EEG) abnormalities (one point for abnormal background without epileptiform discharges, two for abnormal background with epileptiform discharges, three for electrographic seizures and four for status epilepticus)(12). Status epilepticus was defined as continuous seizures or multiple seizures without return to normal level of consciousness lasting greater than 20 minutes. EEG background was included in the score because of its known relationship to seizure risk(19). At the time of hospital discharge, the highest score in each category was used to assign the total score. Since 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 this cohort was enrolled, our center did not perform routine prolonged continuous video-EEG or amplitude integrated EEG. The composite seizure scores were subdivided into three seizure severity categories (no seizures for a score of 0, *mild/moderate* seizures for scores of 1-3 and *severe* seizures for scores ≥4).

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 treated prior to implementation of therapeutic hypothermia at our center.

Magnetic Resonance Imaging

Infants were imaged at a mean age of 5.4 (SD ± 3.0) days using a specialized neonatal head coil on a 1.5Tesla Signa EchoSpeed system (GE Medical Systems). Imaging sequences were optimized for the neonatal brain and included (1) 4 mm (1 mm "gap") sagittal spin-echo (SE) (500/11/2 [TR/TE/excitations]), (2) 4mm (1 mm "gap") axial SE (500/11/2) images, and (3) 4 mm (2mm "gap") axial SE (3000/60,120/1) images through the entire brain. There was no difference in the timing of imaging between the seizure groups (P = 0.2).

The severity of brain injury was measured using conventional T1 and T2 (short and long echo) MRI. Previous work has demonstrated that this provides an accurate measure for brain injury at the ages the infants were imaged. Diffusion-weighted imaging was not available during the early period of the study, and, therefore, was not used for this analysis. A pediatric neuroradiologist who was blinded to the clinical history prospectively evaluated MRI images. Injury to the basal nuclei and the watershed areas was scored independently using a system that is strongly predictive of neurodevelopmental outcome following neonatal encephalopathy(14). The severity of the *basal nuclei* pattern of injury, which primarily evaluates deep gray matter and motor pathway injury, was scored: (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, and (4) more extensive involvement. The severity of the *watershed pattern* injury, which evaluates cortical and white matter injury, was scored: (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, and (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 who was blinded to the neonatal course examined the children at age four 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 and standard deviation of 15, as well as domain scores for Verbal and Performance IQs.

The five-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 children with a score ≥3 have a functional deficit (cerebral palsy).

Statistics

Statistical analysis was performed using Stata 9.2 software (Stata Corp., College Station, Texas). Differences between clinical predictors were assessed using two-tailed student's *t*-test for continuous variables, median or Wilcoxon rank sum for non-parametric data and Chi Square or Fisher exact for categorical variables. Linear and logistic regression analysis were used to evaluate the association between seizure severity and neurodevelopmental outcome. The adjusted analysis accounted for the severity of hypoxic-ischemic brain injury measured on MRI by including both the maximal watershed and basal nuclei scores, each as a categorical predictor in a multivariable regression. We performed two sensitivity analyses: (1) to assess the impact the effect of death within the cohort by imputing the lowest neurodevelopmental scores for children who died prior to evaluation and (2) to account for the fact that we did not include diffusion weighted imaging in this analysis.

RESULTS

One hundred and forty-three infants were enrolled and imaged between November 1996 and June 2003. Of these, 16 died and 77 (61% of the survivors) had complete neurodevelopmental evaluation at age four years. There was no statistical difference in demographic or clinical data between infants who had a complete neurodevelopmental evaluation at age four years compared with those who were lost to follow-up, including infant sex, birth weight and encephalopathy score ($P > 0.1$). Furthermore, surviving children who had a complete evaluation at age four years were no more likely than children who were lost to follow-up to have neonatal seizures (32% vs 38%, $P = 0.4$) or brain injury on MRI (73% vs 72%, $P = 0.9$).

The 16 children who died represented the severe spectrum of hypoxic-ischemic brain injury. Nine (56%) had maximal basal nuclei and watershed scores. All 16 infants had seizures (12 with severe seizures). Eleven (69%) died in the neonatal period following discontinuation of active cardiorespiratory support in the intensive care nursery.

Of the 77 surviving infants followed to age four years, 11 (14.3%) had severe neonatal seizures (composite seizure score ≥4), 14 (18.2%) had mild/moderate seizures (seizure score 1-3) and 52 (67.5%) had no seizures (seizure score 0). Of the 25 infants with seizures, all infants had clinical seizure onset prior to the third day of life (with the exception of a single infant who was paralyzed until day four of life for extracorporeal membrane oxygenation). Two infants (8%) required three or more anti-seizure medications. All of the infants with clinical seizure had an electroencephalogram, which was abnormal in 14 (56%). Recurrent electrographic seizures were present in six cases. Of the infants without clinical seizures, only one had an electroencephalogram, which was normal.

There was no significant difference in birth weight, umbilical cord or first arterial blood gas pH or base excess between the infants with severe or mild/moderate neonatal seizures when compared to those without seizures. There was no apparent difference in the percentage of male infants with seizures compared to those without (64% vs. 50%, $P = 0.25$). The higher

rate of seizures in infants born outside our center was not significant. The lower Apgar scores in infants with seizures were also not significant. Infants with neonatal seizures were more likely to have a higher encephalopathy score (P = 0.002) (Table 1).

The MRI pattern of hypoxic-ischemic injury differed in infants with severe seizures when compared with those with mild/moderate or no seizures (P < 0.0001, Table 2). Of the infants with severe seizures, the basal nuclei predominant pattern was most common (54.6%). Of the infants with mild/moderate seizures, the watershed pattern of injury was most common (50.0%). Infants without seizures were also most likely to have the watershed pattern of injury (55.8%). Four infants had maximal basal nuclei and watershed scores (two with mild/moderate seizures and two with severe seizures).

Of the known predictors of outcome, the severity of hypoxic-ischemic brain injury detected by magnetic resonance imaging and as measured by our scoring system was most highly associated with the cognitive outcome in this cohort. The basal nuclei and watershed scores predicted 39% of the variation in the FSIQ scores, as compared to 25% for the maximal encephalopathy score and 29% for the seizure score (all P < 0.0001).

Unadjusted Analysis

Newborns with seizures in the setting of perinatal asphyxia had worse outcomes than infants without seizures (Table 3). In the unadjusted analysis, for each one-point increase in seizure score, there was a corresponding 6.1-point decrease in the FSIQ (95% CI −8.3 to −3.9). The infants with documented recurrent seizures on EEG had lower FSIQ scores (mean 52 versus 95, P < 0.0001). When seizures were analyzed as a categorical variable, children with severe seizures had, on average, a WPPSI-R FSIQ that was 35.5 points lower than infants without seizures (95% CI −48.8 to −22.1 points), whereas children with mild/moderate seizures had a WPPSI-R FSIQ that was 17 points lower than infants without seizures (95% CI −30 to −5). In the unadjusted analysis, the impact of seizures on the WPPSI-R Performance and Verbal IQs was similar to the effect on the FSIQ.

Children with neonatal seizures were more likely to have an abnormal neurological examination (neuromotor score ≥2) at four years when compared with children with without seizures. The unadjusted odds of a neuromotor score ≥2 were 20.8 (95% CI 5.1-85.0) in children with neonatal seizures when compared to children without seizures. Abnormal neurological examination was present in 7 (63.6%) children with severe neonatal seizures, 7 (50.0%) children with mild/moderate seizures and 3 (5.8%) children without seizures.

Adjusted analysis

The association between seizures and poor neurodevelopmental outcome persisted after adjusting for the severity of hypoxic-ischemic brain injury as measured by the basal nuclei and watershed scores on MRI (Table 3). In the adjusted analysis, for each one-point increase in seizure score, there was a corresponding 4.7-point decrease in the FSIQ (95% CI −7.2 to −2.2). The effect of documented recurrent seizures on EEG also persisted after adjusting for injury on MRI, with and average FSIQ that was 33.0 points lower (95% CI −50.9 to −15.0). When seizures were analyzed as a categorical variable, infants with severe neonatal seizures had average adjusted WPPSI-R FSIQ scores that were 29.7 points lower (95% CI −45.2 to −14.2 points), while infants with mild/moderate seizures had scores that were 14.2 points lower (95% CI −26.5 to −1.9 points) when compared to infants without seizures. The adjusted impact of seizures on the WPPSI-R Performance and Verbal IQs was similar to the effect on the FSIQ. The association between seizure severity and adverse cognitive outcome was not modified by the predominant pattern of injury (i.e. basal nuclei vs. watershed) or by the severity of the basal nuclei or watershed injury.

The association between neuromotor outcome and seizures also persisted after adjusting for the severity of injury measured on MRI, with an odds of neuromotor score ≥2 at 20 (95% CI 3 – 140) for children with neonatal seizures when compared to those without seizures.

Sensitivity Analyses

We performed sensitivity analyses to examine the effect of death and timing of imaging on the results. In order to account for deaths in the data set, we imputed the lowest FSIQ and a neuromotor score of 6 for those children who died prior to neurodevelopmental testing at age four years and found that magnitude of the effect of severe or mild/moderate seizures was similar and the results remained highly significant.

Because imaging changes before the third day of life are best measured using diffusion weighted imaging(18,21), but this technique was not available for all infants in this study, we performed sensitivity analysis to restrict the results to the 52 infants who were imaged after this time. Again, we found that effect of severe or mild/moderate seizures was similar, however the P-value was 0.06, reflecting the smaller sample size.

DISCUSSION

We show for the first time that the association between clinical neonatal seizures treated according to local standard of care, and adverse long-term neurodevelopmental outcome in infants with neonatal encephalopathy, is independent of the severity of hypoxic-ischemic brain injury. After adjusting for the severity of hypoxic-ischemic brain injury as measured by MRI, infants with clinical seizures had a dramatically worse age four full-scale intelligence quotient on the WPPSI-R than children without neonatal seizures. The effect varied with the severity of the seizures: children with *severe* neonatal seizures had adjusted scores that were, on average, two standard deviations lower than children without neonatal seizures, whereas children who suffered only *mild/moderate* neonatal seizures had scores that were only one standard deviation below those of their peers without seizures.

Our findings are supported by animal models, which show that seizures damage the immature brain, especially in the setting of hypoxia-ischemia. Rat pups exposed to hypoxia-ischemia *and* kainic acid-induced seizures had preferential injury to the hippocampus and high levels of glutamate(22,23). Furthermore, even healthy rat pups who suffered recurrent seizures were significantly worse than controls in neurobehavioral tasks, indicating impaired learning, memory and activity level(24) (25-27). The mechanisms for these deficits are unknown, but may relate to reduced density of dendritic spines in hippocampampal pyramidal neurons(28), delayed neuronal loss(29), decreased neurogenesis(30) or changes in hippocampal plasticity such as decreased capacity for long-term potentiation, reduced susceptibility to kindling and enhanced paired-pulse inhibition(25).

Despite robust results and blinded study design, a possible alternative explanation for the adjusted association between neonatal seizures and adverse outcome is residual confounding from unmeasured brain injury. In our adjusted analysis, we used validated scales to assess for the degree of both basal nuclei and watershed injury visible on T1 and T2-weighted MR images. Unmeasured injury -- for example to the hippocampus, which is difficult to image, yet important in both epileptogenesis and cognitive outcome – could account for both the seizures and the poor neurodevelopmental outcome. However, MRI is currently the best known method for measuring the severity of brain injury following perinatal hypoxia-ischemia, and the basal nuclei and watershed scales are highly correlated with cognitive and neuromotor outcomes in this cohort. Furthermore, the effect of seizures was unchanged in the sensitivity analyses, and the outcome was similar in each pattern of brain injury. Finally, it is impossible to differentiate the effect of the seizures themselves from the effects of

standard medical management using anti-seizure medications such as phenbarbital and phenytoin, which have neurotoxic effects in experimental animal models(8).

This study includes a large cohort, high quality neuroimaging and long-term outcomes to address the question of the impact of seizures on neurodevelopment in infants with hypoxic-ischemic brain injury. The data are limited by our ability to precisely measure the severity of seizures, particularly electrical seizures without clinical accompaniment, and to confirm that clinical seizures represent true electrographic seizures. We found that 11 of the 25 infants with clinical seizures had a normal EEG, which may be due to a number of reasons. First, some newborns may have had clinical seizure types with inconsistent association to EEG findings (such as motor automatisms or myoclonic seizures). Second, medication given prior to the EEG may have resulted in seizure resolution. Finally, infants had routine screening EEGs rather than long term monitoring, making it likely that some seizures went undetected (at the time of this study, our center had no standard protocol for timing and duration of continuous EEG monitoring of infants at risk for seizures). The seizure score reflects the number and refractoriness of seizures, as well as the degree of electroencephalographic abnormality. Past studies have shown that infants with seizures that respond to phenobarbital typically have a lower seizure burden and relatively normal EEG background(31), making our categorization into three levels (none, mild/moderate or severe) clinically relevant. Our seizure measurements reflect standard of care at our center at the time this cohort was enrolled and contemporary standard of care in most centers.

Using MRI as a sensitive measure of the degree of hypoxic-ischemic brain injury, we can now start to differentiate between the overlapping adverse effects of the hypoxic-ischemic brain injury and early seizures in human infants. We showed that infants with clinical neonatal seizures in the setting of neonatal encephalopathy had worse long-term neurodevelopmental outcome that was independent of the degree of hypoxic-ischemic brain injury. This is consistent with our previous observation that impaired brain metabolism in the setting of seizures (high lactate and lower N-acetylaspartate levels) is independent of the degree of injury measured on MRI(12).

Understanding how seizures impact the developing brain has enormous therapeutic implications. Newborns in this cohort were treated for “clinical” seizures, reflecting contemporary practice at the time of enrollment. There is no good evidence, and thus no widely accepted clinical consensus regarding appropriate therapy for seizures in newborns, especially in the case of electrographic seizures without clinical correlate and seizures identified by amplitude-integrated EEG. With the rapid uptake of prolonged cortical monitoring methods, further studies will be imperative to determine the relative impact of seizures that are electrographic only, as well as whether treating seizures more aggressively has a long-term beneficial neurodevelopmental effect.

Our data suggest that clinical neonatal seizures and their treatment are associated with adverse long-term cognitive and neuromotor outcome in children at risk for perinatal asphyxia that is independent of sensitive MRI measures of hypoxic-ischemic injury. Having accounted for the severity of hypoxic-ischemic injury, the worsening neurodevelopmental outcome with increasing seizure severity in our cohort is keeping with the hypothesis that the seizures themselves may impair the developing human brain. While our findings are consistent with experimental evidence, further work is necessary -- both in animal models and in humans -- to determine the mechanisms by which seizures could impair the developing brain and to determine if differences in seizure treatment can improve neurodevelopmental outcome.

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Table 1

Clinical characteristics by seizure severity of 77 infants at risk for perinatal hypoxic-ischemic brain injury followed to age four years

	Severe Seizures N = 11	**Mild/Moderate Seizures N = 14**	**No Seizures N = 52**	**P***
Birth weight, *mean (± SD grams)*	3406 (±759)	3401 (±474)	3229 (±533)	0.4
Male, *N (%)*	7 (64)	9 (64)	26 (50)	0.5
Outborn, *N (%)*	1 (9)	4 (29)	4 (8)	0.08
5-minute Apgar, *median (IQR)*	3 (2-5)	5 (4-5)	5 (4-7)	0.06
Cord or first arterial blood pH, *mean (± SD)*	7.09 (±0.13)	7.12 (±0.13)	7.08 (±0.17)	0.7
Cord or first arterial base excess, *mean (± SD)*	−14.4 (±5.0)	−10.5 (±4.9)	−11.3 (±6.1)	0.2
Maximal encephalopathy score, *median (IQR)*	6 (5-6)	5 (4-6)	3 (2-5)	0.002

* F-test for continuous variables, median, chi square or Fischer exact for categorical variables

Table 2

Predominant pattern of injury by seizure severity in 77 infants at risk for perinatal hypoxic-ischemic brain injury followed to age four years

	Severe Seizures N = 11	**Mild/Moderate Seizures N = 14**	**No Seizures N = 52**
Pattern of injury, N (%)			
No Injury	1 (9.1)	1 (7.1)	19 (36.5)
Basal nuclei pattern	6 (54.6)	6 (42.9)	4 (7.7)
Watershed pattern	4 (36.4)	7 (50.0)	29 (55.8)

Fischer exact P<0.0001

Table 3

Full-scale intelligence quotient (FSIQ) on the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) at age four years by seizure severity in 77 children at risk for perinatal hypoxic-ischemic brain injury

	Severe Seizures N = 11	**Mild/Moderate Seizures N = 14**	**No Seizures N = 52**	**P***
WPPSI-R FSIQ *mean (95% CI)*				
-Unadjusted	64.7 (52.6 – 76.9)	83.1 (72.4 – 93.9)	100.2 (94.6 – 105.8)	<0.0001
-Adjusted**	67.2 (54.6 – 79.8)	82.7 (72.7 – 92.7)	96.9 (90.7 – 103.1)	0.001

* F test

** Scores were adjusted for the severity of brain injury as measured by basal nuclei and watershed scores on MRI.