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Risk Factors For Epilepsy In Children With Neonatal Encephalopathy

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Abstract

We examined neonatal predictors of epilepsy in term newborns with neonatal encephalopathy (NE) by studying children enrolled in a longitudinal, single center cohort study. Clinical data were obtained through chart review, and MRI was performed in the neonatal period. We administered a seizure questionnaire to parents of children aged ≥12 months (range 12 months–16.5 years) to determine the outcome of epilepsy. The association between clinical predictors and time to onset of epilepsy was assessed using Cox proportional hazards regression. Thirteen of 129 children developed epilepsy: all had neonatal seizures and brain injury on neonatal MRI. Of the newborns with neonatal seizures, 25% (15.8/1000 person-years) developed epilepsy, with the highest hazard ratios (HR) in the newborns with status epilepticus (HR 35.8, 95% CI 6.5 –196.5). Children with severe or near-total brain injury were more likely to develop epilepsy compared with those with only mild or moderate injury (HR 5.5, 95% CI 1.8–16.8). In a multivariable analysis adjusting for degree of encephalopathy and severe/near total brain injury, status epilepticus was independently associated with epilepsy. These data add to information regarding epilepsy pathogenesis, and further aid clinicians to counsel parents regarding the likelihood that a newborn with NE will develop epilepsy.

Introduction

The incidence of neonatal encephalopathy (NE) is about 1 to 2.5 per 1000 live term births, mostly as a result of perinatal asphyxia (1–3). NE is a significant cause of neonatal death and adverse neurodevelopmental outcome such as cerebral palsy, developmental delay, and epilepsy. The reported rate of epilepsy following NE due to hypoxic-ischemic encephalopathy ranges from 9% to 33%(4–6) and in one study, children with a history of hypoxic-ischemic encephalopathy had five times the risk of developing epilepsy when compared with those without(7).

Though children with NE are known to be at risk for epilepsy, there are few studies examining the neonatal risk factors for developing seizures beyond the newborn period. Past studies in small cohorts have examined severity of encephalopathy, neonatal seizures, and magnetic resonance imaging (MRI) as risk factors with conflicting results. Pisani *et al* found that severe (but not moderate) encephalopathy was associated with later epilepsy, whereas van Koijj *et al* found a 10% prevalence of epilepsy among a cohort of children who suffered

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moderate encephalopathy(4,6). Neonatal seizures were a risk factor in one study, although the effect was not significant after adjusting for the degree of encephalopathy(4). MRI injury is also risk factor for epilepsy(5,6). Small cohort size, inadequate neonatal imaging or lack of long-term outcome data limit these studies, and counseling for parents of children with NE remains a challenge.

The objective of this study was to evaluate the neonatal clinical and imaging risk factors for childhood epilepsy in a single center cohort of children with a history of neonatal encephalopathy. All children were imaged using high resolution MRI according to a standardized research protocol in the newborn period, and evaluated longitudinally through childhood.

Materials and Methods

This is a longitudinal cohort study of neonates who were admitted to the Intensive Care Nursery at the University of California San Francisco. Newborns met inclusion criteria of gestational age ≥ 36 weeks at birth *and* any one of the following: umbilical cord arterial blood pH < 7.1, umbilical cord arterial blood base excess > −10, or five 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(8–14). Newborns were excluded if there was evidence of intrauterine or perinatal infection, major anomalies of the brain or other major organ system, or evidence of congenital metabolic disease.

From December 1993 to June 2009, 234 infants ≥ 36 weeks gestational age at birth were enrolled and imaged according to protocol. Thirty-one children were excluded for the following reasons: deceased during the birth admission (17 children), or withdrew from the study (14 children), leaving 203 subjects.

Clinical data

Trained neonatal research nurses extracted birth delivery data including gestational age at birth, birth weight, and Apgar scores from medical records. Clinical seizures (spells identified by the attending physician as seizures and treated using anti-convulsant medication), electrographic seizures (events identified by the attending neurophysiologist as seizures), and status epilepticus (recurrent electrographic seizures considered by the neurophysiologist as “status epilepticus, “continuous” or “near continuous” seizures) were determined from chart review. Prior to 2008, video-EEG monitoring was performed at the discretion of the attending neurologist and neonatologist and performed as standard of care in all children with clinical seizures (minimum duration 30 minutes). Since 2008, video-EEG has been performed for all newborns treated with therapeutic hypothermia from the time of admission until 6–12 hours after rewarming and at least 24 hours after the last recorded EEG seizure. A pediatric neurologist measured the degree of encephalopathy in the first 3 days of life on a scale of 0–6, which considers feeding, alertness, tone, respiratory status, reflexes, and seizures(12).

Magnetic Resonance Imaging

All neonates were imaged with MRI using a specialized neonatal head coil on a 1.5Tesla Signa EchoSpeed system (GE Medical Systems), and using imaging sequences optimized for the neonatal brain(14,15). In cases where more than one MRI was performed during the hospital stay, the MRI closest to day of life 3 to 5 was used for analysis. A pediatric neuroradiologist blinded to the neonatal course prospectively scored the imaging as previously described(8). Injury was scored using a system that is strongly predictive of

neurodevelopmental outcome following neonatal encephalopathy(8). The pattern of injury was described as “basal ganglia/thalamus predominant,” “watershed predominant,” or “normal”(11). We defined “mild-moderate injury” as a basal ganglia/thalamus of 1 or 2 (abnormal signal in the thalamus and/or lentiform nucleus), or watershed pattern of 1–4 (abnormal signal in the anterior and/or posterior watershed zones), and “severe injury or near-total injury” as a basal ganglia/thalamus score ≥ 3 or a watershed score of 5 (more extensive involvement in either territory).

Epilepsy Interview

The parents of enrolled subjects were contacted by telephone in June 2010, and administered a structured seizure questionnaire that was developed for the purpose of this study. For the children with postneonatal seizures, parents were asked to provide information regarding age of seizure onset, frequency, and medication use. Epilepsy was defined as recurrent, unprovoked seizures, or a single seizure in the setting of abnormal EEG and initiation of medication. For the children who died following hospital discharge, the medical records were reviewed in order to complete the standardized seizure questionnaire. Epilepsy was graded according to modified Engel classification (Class 0 = seizure-free and off seizure medications for at least six months; Class 1 = seizure-free for at least six months while on medication or seizure-free off medication for fewer than six months; Class 2 = fewer than one seizure per month on medication; Class 3 = one to four seizures a month on medication; Class 4 = five to thirty seizures per month on medication; Class 5 = thirty or more seizures a month)(16).

Neurodevelopmental Follow-Up

A pediatric neurologist and a developmental psychologist who were blinded to the neonatal course examined the children at ages 3–6 months, 1 year, 2.5 years, 4 years, and 8 years. Neuromotor function was evaluated using the neuromotor score, a five point scale where 0 is normal and 5 is spastic quadriparesis(8). The neuromotor score was classified as follows: 0 or 1 normal, 2 borderline, ≥3 abnormal, and 5 spastic quadriparesis as well as cranial nerve involvement. An age appropriate neuropsychological test was administered to the child at each follow-up appointment. The Bayley Scales of Infant Development were used to test children at one year and 2.5 years (Bayley-II prior to 2008) (17,18). At the age of four, the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) was used(19,20). The Wechsler Intelligence Scale for Children IV (WISC-IV)(21) was administered for the eight-year follow-up. Scores from standardized tests (all with a mean of 100 and a standard deviation of 15) were used to classify cognitive outcomes as follows: ≥85 on all subscales was considered normal, 70–84 on one or more subscales was considered borderline, and <70 (that is, 2 SDs below the mean) on one or more subscales was considered abnormal. Co-morbitidies and most recent neurological and neurodevelopmental exams were extracted from medical records and structured seizure questionnaire.

Analysis

Data analyses were conducted using statistical software Stata 10 (StataCorp LP, College Station, Texas). The association of clinical predictors with time to onset of epilepsy was assessed using Cox proportional hazards regression, and graphically displayed using Kaplan-Meier curves. Data were censored at the time of onset of epilepsy, or at the time of the telephone interview in children without epilepsy. Differences between children with and without follow-up were assessed using two-tailed Student’s *t*-test for continuous variables, Wilcoxon rank sum for non-parametric data, and chi-square or Fisher’s exact test for categorical variables. Multivariable model included those predictors with p-value ≤0.1 in the univariable analysis. *P* values < 0.05 were considered significant.

The Committee on Human Research at the University of California, San Francisco, approved the protocol. Infants were studied only after informed voluntary parental consent.

Results

Of the 203 subjects included in the study, we successfully contacted 127 families by telephone and were able to complete adequately adjudicate outcome based on medical records for 2 deceased children, for an overall follow-up rate of 64%. The study subjects are presented in Table 1. The children whose parents were not available to complete the survey were similar to those whose parents did complete the survey with no differences in sex, gestational age at birth, birth weight, cord gas pH or base excess, neonatal encephalopathy score, and MRI injury scores. However, those whose parents responded were significantly more likely to have had neonatal seizures (40% vs 25%, p=0.04) and have been enrolled in the study more recently (median year of enrollment 2004 vs 1997, p<0.00005).

The median age of surviving study participants at the time of the follow-up survey was 73 months (6 years, range 12 months to 16.5 years).

Epilepsy Features and Outcome

Of the 129 evaluated subjects, 13 (10%) developed epilepsy, 7 had febrile seizures, and 1 child had a single spell at age two months that was not clearly a seizure. The age of epilepsy onset ranged from 0 to 5 years, of which 7 (54%) had onset within the first year of life, and all had adverse neurodevelopmental outcomes. The clinical characteristics of the 13 study subjects with epilepsy are presented in Table 2.

Perinatal Risk Factors for Epilepsy

Degree of encephalopathy was the only clinical feature associated with epilepsy (Table 3).

Neonatal Seizures and Risk of Epilepsy

All 13 children with epilepsy had a history of clinical and/or electrographic neonatal seizures. The frequency of epilepsy among the 52 children with a history of neonatal seizures was 25% (or 15.7 per 1000 person years). Among children with neonatal seizures, those with status epilepticus were most likely to develop epilepsy (5/6, 83% or 1237.1/1000 person-years). The single child who had not developed epilepsy was 21 months at the time of the evaluation and had been treated with therapeutic hypothermia. Those children without status, but whose neonatal seizures EEG confirmed were more likely to develop epilepsy as compared with those who had only clinical seizures (5/19, 26% or 93.5/1000 person-years vs 3/28, 11% or 14.5/1000 person-years; hazard ratio, HR, 4.0, 95% CI 0.9–17.3). The epilepsy-free survival data in those children with and without a history of neonatal seizures are presented in Figure 1.

Brain Injury and Epilepsy

All children with epilepsy had injury on neonatal MRI, and the severity of injury was associated with epilepsy. The children with severe or near-total brain injury were most likely to develop epilepsy (8/22, 36% or 54.7/1000 person-years) vs. 5/65 (8% or 11.5/1000 person-years) for those with mild or moderate injury. Of the 16 children with severe or near-total brain injury *and* neonatal seizures, half developed epilepsy. Pattern of injury was also important: of the 30 children with basal ganglia/thalamus predominant pattern of injury, 6 (20% or 32.3/1000 person-years) developed epilepsy, whereas only seven (12%, 17.7/1000 person years) with watershed predominant pattern of injury developed epilepsy (p=0.005). When compared to those children with mild/moderate brain injury, those with severe or near

total injury had a higher rate of epilepsy (HR 5.5, 95%CI 1.8 – 16.8, p = 0.003). Epilepsy-free survival by severity of brain injury is presented in Figure 2.

Adjusted Analysis

In a multivariable analysis among those with moderate or severe encephalopathy, neonatal seizures and MRI injury, adjusting for neonatal encephalopathy, status epilepticus remained a highly significant risk factor for epilepsy (HR 17.3, 95%CI 2.7 – 110.0, p=0.003), whereas severe/near total injury (HR 2.4, 95%CI 0.7 – 8.4, p=0.2) was not (Table 4).

Discussion

In this longitudinal sample of 129 newborns with neonatal encephalopathy, neonatal seizures and brain injury on MRI were strong risk factors for epilepsy, and the children with epilepsy all had adverse neurodevelopmental outcome.

These results support previous studies suggesting that epilepsy occurs in children with a more severe spectrum of NE. The 25% frequency of epilepsy following neonatal seizures is similar to previous contemporary cohorts that used broad clinical and/or electrographic definitions for neonatal seizures, and lower than studies that required EEG confirmation of seizures(22–25). Although duration of follow-up is variable across studies, highest risk within the first year of life is a common feature, as is the high rate of associated neurodevelopmental disabilities(23,25–28).

Animal studies have begun to elucidate mechanisms by which neonatal seizures can induce persistent enhanced neocortical excitability(29). Our data also support evidence that severity of seizures is important, which is in keeping with studies by Clancy and Legido, who showed in a mixed cohort that a higher burden of neonatal seizures was a risk factor for epilepsy(22), and Pisani *et al*, who showed a higher rate of epilepsy after status epilepticus when compared with recurrent seizures(30).

Severity and pattern of MRI injury are known risk factors for neonatal seizures(6,11), and we also show a clear relationship with epilepsy. Children with severe basal ganglia/thalamus pattern of injury and cortical involvement were at highest risk of developing epilepsy. There is controversy from animal studies regarding whether neuronal injury is required for acquired epileptogenesis in the immature brain, or whether seizures alone without neuronal injury can cause changes in excitability sufficient to result in unprovoked seizures beyond the neonatal period(31). Our finding, that epilepsy occurred only in those children with apparent brain injury on MRI supports, but does not prove, the hypothesis that neuronal injury is, in fact, required to develop epilepsy.

Though our findings do not support a reduced risk of epilepsy in the cooled subjects, the data we present do not exclude this possibility. Since fall 2007, we have treated most newborns at risk for hypoxic-ischemic injury and moderate-severe encephalopathy with therapeutic hypothermia using whole body cooling. Therapeutic hypothermia, which has been shown to reduce death and disability at 18–22 months in several randomized, controlled trials(32–35) also has an anti-seizure effect in animal models(36,37), although its effect on seizures in human newborns is not clear. Among newborns treated with therapeutic hypothermia at our center, electrographic seizures are present in more than 30%. If neonatal seizures are suppressed in human newborns treated with hypothermia, and neonatal seizures enhance long-term epileptogenesis, the risk of epilepsy in the cooled population may ultimately be reduced. The question of whether hypothermia reduces neonatal seizure burden and/or epileptogenesis should be further explored in larger data sets.

Although this is a large cohort with high-quality neonatal imaging and long-term follow-up, the data are limited in several ways. First, the survey response rate was only 64%. This limitation may have led to an overestimate of the prevalence of epilepsy, since the rate of neonatal seizures was higher in those children whose parents responded to the interview. However, response rate should not affect the relationships between perinatal risk factors, including seizures and MRI findings, and epilepsy. Second, it is possible that there was bias towards diagnosis of epilepsy in some cases of children with ambiguous spells and severe developmental impairment. This may have falsely increased the relationship between MRI injury and neonatal seizures, and epilepsy. Third, since the study's inception in 1993, we have changed the guidelines for monitoring and treating newborns with encephalopathy. Prior to 2008, video-EEG was used at the discretion of the attending neurologist, usually for 30–60 minute routine recordings. Since 2008, we have monitored all children with NE using continuous video-EEG for the duration of hypothermia and rewarming. In order to understand the true relationship between clinical vs. electrographic seizures and epilepsy, we will need to examine a larger cohort of subjects with long-term conventional video-EEG monitoring.

Conclusions

Epilepsy is an outcome following brain injury and neonatal seizures in the setting of severe hypoxic-ischemic brain injury. These data add to our understanding of the pathogenesis of epilepsy following seizures in the newborn period, and provide information for clinicians and parents planning long-term care for children with NE. For term infants with NE, but without both neonatal seizures and brain injury on MRI, parents can be reassured that the child is unlikely to develop epilepsy. Children with electrographic seizures (especially status epilepticus) and severe brain injury have a high risk of adverse neurodevelopmental outcome, including epilepsy. This high-risk population will be important for future studies examining neuroprotective and anti-epileptic agents. Neonatal seizures and status epilepticus are potentially modifiable risk factors, and there is urgent need for studies to examine whether early monitoring and treatment will improve outcome.

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Abbreviations

HR	Hazard ratio
NE	Neonatal encephalopathy
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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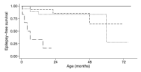

Figure 1.
Kaplan-Meier estimates for epilepsy-free survival among 129 newborns with neonatal encephalopathy, with and without neonatal seizures. No seizures: *solid line* (N=76); clinical seizures only: *dashed line* (N=28), EEG confirmed seizures: *dotted line* (N=19); status epilepticus: *dash-dot line* (N=6).

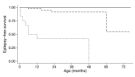

Figure 2.
Kaplan-Meier estimates for epilepsy-free survival among 129 newborns with neonatal encephalopathy, with and without brain injury. No injury: *solid line* (N=42); mild/moderate injury: *dashed line* (N=65); severe/near total injury; *dotted line* (N=22).

Table 1

General clinical characteristics among 129 children with neonatal encephalopathy.

Perinatal Characteristics	
Male sex	72 (56%)
Gestational age at birth, *weeks*	39.5 (±1.6)
Birth weight, *grams*	3331 (±617)
Cesarean section	65 (50%)
5 minute Apgar score*	
≥6, N(%)	37 (29%)
4–5, N(%)	45 (35%)
0–3, N(%)	46 (36%)
Degree of encephalopathy	
Mild	29 (22%)
Moderate	41 (32%)
Severe	59 (46%)
Therapeutic Hypothermia	31 (24%)
Neonatal seizures	
No seizures	76 (59%)
Clinical only	28 (22%)
EEG confirmed seizures	19 (15%)
Status epilepticus	6 (5%)
MRI injury	
No injury	42 (33%)
Mild/moderate	65 (50%)
Severe/near-total	22 (17%)

Data are presented as N(%), mean (standard deviation) or median (range)

*Data missing for one subject

Table 2

Clinical, seizure and MRI characteristics, neurodevelopmental outcome for 13 children with neonatal encephalopathy and childhood epilepsy.

	Neonatal Evaluation		Follow-Up	
Age and Gender	**Neonatal seizures**	**MRI**	**Epilepsy**	**Neurodevelopmental outcome***
Deceased Male	• Clinical and electrographic; status epilepticus	• Near-total brain injury	*Class 5* • Onset unknown • Daily seizures refractory to phenobarbital, clonazepam, valproic acid, gabapentin, primidone, ketogenic diet	Age 2 • Bayley II MDI – 49 • NMS 5
14 year old male	• Clinical and electrographic; status epilepticus	• Single focal abnormality (Watershed pattern)	*Class 1* • Onset 15 months Carbamazepine monotherapy	Age 10 • WISC FSIQ - 49 • NMS 0
13 year old female	• Clinical only	• Near-total brain injury	*Class 1* • Onset 4 years • Levetiracetam monotherapy	Age 4 • WPPSI-R FSIQ - 49 • NMS 5 • Cortical visual impairment
13 year old male	• Clinical and electrographic; status epilepticus	• Abnormal signal in the thalamus, lentiform nucleus and perirolandic cortex • Abnormal signal in both anterior and posterior watershed zones (Watershed pattern)	*Class 1* • Onset before 1 month • Levetiracetam monotherapy	Age 4 • WPPSI-R FSIQ - 49 • NMS 5
12 year old male	• Clinical and electrographic	• Abnormal signal in the thalamus, lentiform nucleus and perirolandic cortex (Basal ganglia/thalamus pattern)	*Class 0* • Onset before 1 month • Infantile spasms • Not on AED	Age 4 • WPPSI-R FSIQ - 49 • NMS 5 • Dystonia, cortical visual impairment
11 year old male	Clinical and electrographic	• Abnormal signal in both anterior and posterior watershed zones (Watershed pattern)	*Class 0* • Onset 6 months • Not on AED	Age 2 • Bayley II MDI - 49 • NMS 5

Age and Gender	Neonatal Evaluation		Follow-Up	
	Neonatal seizures	**MRI**	**Epilepsy**	**Neurodevelopmental outcome***
				• Cortical visual impairment
11 year old male	Clinical and electrographic; status epilepticus	• Abnormal signal in both anterior and posterior watershed zones, plus more extensive involvement (Watershed pattern)	*Class 1* • Onset 4 months • Phenobarbital monotherapy	Age 4 • WPPSI-R FSIQ - 49 • NMS 5
10 year old female	Clinical and electrographic	• Abnormal signal in the thalamus and lentiform nucleus (Basal ganglia/thalamus pattern)	*Class 2* • Onset 5 years • Levetiracetam monotherapy	Age 5 • WPPSI-R FSIQ - 49 • NMS 5 • Dystonia
8 year old female	Clinical and electrographic	• Abnormal signal in the thalamus • Abnormal signal in both anterior and posterior watershed zones (Watershed pattern)	*Class 2* • Onset 5 years • Phenytoin monotherapy	No follow up
5 year old male	Clinical only	• Near-total brain injury	*Class 5* • Onset 6 months • Infantile spasms • Zonisamide monotherapy	Age 6 months • NMS 5 • Cortical visual impairment, G-tube fed
2.5 year old male	Clinical only	• Abnormal signal in anterior or posterior watershed white matter (Watershed pattern)	*Class 1* • Onset 22 months • Oxcarbazepine monotherapy	Age 2.5 year • Bayley III cognitive 80 • NMS 2
2 year old female	Clinical and electrographic; status epilepticus	• Near-total brain injury	*Class 2* • Onset 2 months • Valproic acid monotherapy	Age 1 • Bayley III cognitive 55 • NMS 5 • Cortical visual impairment
2 year old female	Clinical and electrographic	• Abnormal signal in both anterior and posterior watershed zones, plus more extensive	*Class 2* • Onset 12 months	Age 1 • Bayley III cognitive 55

Age and Gender	Neonatal Evaluation		Follow-Up	
	Neonatal seizures	**MRI**	**Epilepsy**	**Neurodevelopmental outcome***
		involvement (Watershed pattern)	• Levetiracetam monotherapy	• NMS: 5 • G-tube fed

Bayley II/III Bayley Scales of Infant Development, 2nd and 3rd edition; **MDI** Mental Developmental Index; **WISC** Wechsler Intelligence Scale for Children; **WPPSI-R** Wechsler Preschool and Primary Scale of Intelligence-Revised; **FSIQ** Full Scale Intelligence Quotient; **AED** anti-epileptic drug; **NMS** neuromotor score; **G-tube** gastrostomy tube

*__Neurodevelopmental performance__: Scores are from the last evaluation administered. All tests have a mean of 100 and a standard deviation of 15. A score of 49 denotes extremely poor performance more than 3 standard deviations or lower, or untestable.

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Table 3

Incidence rate and hazard ratios for epilepsy risk factors among 129 children with neonatal encephalopathy.

	Person- years	Epilepsy cases	Incidence rate/1000 person-years (95% CI)	HR (95% CI)	P
Perinatal Characteristics					
Sex					
- Females	381	5	13.1 (5.5 – 31.6)	-	
- Males	444	8	18.0 (9.0 – 36.1)	1.3 (0.4–4.1)	0.6
Delivery Method					
- Vaginal delivery	468	9	19.2 (10.0 – 37.0)	-	
- Cesarean section	356	4	11.2 (4.2 – 29.9)	0.5 (0.2–1.6)	0.2
5 minute Apgar score					
≥6, N(%)	305	2	6.6 (1.6 – 26.2)	-	
4–5, N(%)	280	6	21.5 (9.6 – 47.8)	2.8 (0.6 – 18.8)	
0–3, N(%)	238	5	21.0 (8.7 – 50.5)	2.5 (0.5 – 12.8)	0.4
Degree of encephalopathy (N = 100)[*]					
Moderate	305	1	3.3 (0.5 – 23.2)	-	
Severe	267	12	45.0 (25.5 – 79.2)	10.7 (1.4 – 82.7)	0.002
Therapeutic Hypothermia					
Not treated	774	11	14.2 (7.9 – 25.7)		
Treated	51	2	39.4 (9.9 – 157.6)	0.9 (0.2 – 4.1)	0.8
Neonatal seizures (N=53)[**]					
Clinical only	206	3	14.6 (4.7 – 45.1)	-	
EEG confirmed seizures	53	5	93.5 (38.9 – 224.7)	4.0 (0.9 – 17.3)	
Status epilepticus	4	5	1237.1 (514.9 – 2972.2)	35.8 (6.5 – 196.5)	0.0001
MRI injury (N = 87)[§]					
Mild/moderate	434	5	11.5 (4.8 – 27.7)	-	
Severe/near-total	146	8	54.7 (27.4 – 109.4)	5.5 (1.8 – 16.8)	0.003

[*] No cases of epilepsy among children with mild neonatal encephalopathy;

[**] No cases of epilepsy among children without neonatal seizures;

[§] No cases of epilepsy among children without injury on neonatal MRI.

Table 4

Adjusted risk of epilepsy among those newborns with MRI injury, neonatal seizures and moderate or severe neonatal encephalopathy (N=42).

	Adjusted HR (95% CI)	P
Severe encephalopathy	4.5 (0.5 – 40.6)	0.2
Severe/Near total brain injury	2.4 (0.7 – 8.4)	0.2
EEG confirmed seizures	4.1 (0.8 – 21.0)	0.09
Status epilepticus	17.3 (2.7 – 110.0)	0.003