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Pattern of Brain Injury Predicts Long-Term Epilepsy Following Neonatal Encephalopathy

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Abstract

Objective: To determine if patterns of hypoxic-ischemic brain injury on magnetic resonance imaging (MRI) in term newborns predict subsequent childhood epilepsy. **Methods**: This retrospective cohort study includes term newborns with encephalopathy (n = 181) born between 2004-2012 and admitted to British Columbia Children's Hospital. MRI was performed between 3 and 5 days of age. The predominant patterns of hypoxic-ischemic injury were classified as Normal, Watershed, Basal Nuclei, Total, and Focal-Multifocal. Lesions in hippocampus, motor and occipital cortex were noted. **Results:** Of 181 newborns, 166 (92%) survived the neonatal period, and 132 (80%) had follow-up with a median duration of 61 months (IQR: 28–95). Twenty-three children (17%) developed epilepsy. A higher proportion with Watershed, Basal Nuclei, or Total patterns developed epilepsy ($P < .001$). Injury to motor cortex, hippocampus, and occipital lobe ($P < .01$) were independent risk factors for epilepsy. In the adjusting logistic model, Watershed (odds ratio = 16.0, 95% CI [1.3, 197.2], $P = .03$) and Basal Nuclei injury (odds ratio = 19.4, 95% CI [1.9, 196.3], $P = .01$) remained independent risk factors. Therapeutic hypothermia did not alter these associations. Severity of brain injury and recurrent neonatal seizures are other clinical risk factors. **Significance:** In term newborns with hypoxic-ischemic encephalopathy, the predominant pattern of Watershed and Basal Nuclei injury are valuable predictors for development of epilepsy in later childhood.

Keywords

electroencephalography, hypoxic-ischemic encephalopathy, neonatal seizures, magnetic resonance imaging, epilepsy, children

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Neonatal encephalopathy, a "clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant,"[1] often follows moderate or severe hypoxic ischemic injury.[2,3] Hypoxic ischemic encephalopathy carries significant risks for neonatal death and adverse neurodevelopmental outcome: it is estimated that as many as 10-60% of affected infants die during the neonatal period and about 25% of survivors have long-term neurodevelopmental sequelae.[4,5] The reported rate of epilepsy in survivors of hypoxic ischemic encephalopathy ranges between 9 and 33%.[6,7] Although newborns with hypoxic ischemic encephalopathy are 5 times more likely to develop epilepsy later in childhood,[8] few studies have examined neonatal risk factors for developing childhood epilepsy. Previous studies report that the severity of encephalopathy and the occurrence of neonatal seizures are the most significant predictors for childhood epilepsy.[6,7,9] In earlier studies, hypoxic ischemic brain injury on magnetic resonance imaging (MRI) was predictive for neonatal

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seizures[7,10] and development of later epilepsy.[6,11,12] However, in these studies the timing of neuroimaging was not uniform and injury to specific anatomical structures was not assessed. Hypoglycemia also often occurs in the context of neonatal encephalopathy resulting in brain injury, predominantly affecting the posterior white matter, optic radiations and pulvinar.[11,13,14] There are few studies limited by small sample size which examine the risk of neonatal seizures and childhood epilepsy following neonatal hypoglycemia with radiological manifestations.[13,15]

The objectives of this retrospective study of a cohort of term newborns with hypoxic ischemic encephalopathy all of whom had MRI scans between day 3-5 of life were (1) to determine whether the predominant patterns of hypoxic ischemic injury and specific anatomical lesions are predictive for later childhood epilepsy, and to evaluate their association with neonatal seizures. (2) to determine whether hypoglycemia with MRI abnormalities is predictive for childhood epilepsy.

Methods

Study Population

This retrospective cohort study was approved by the University of British Columbia Clinical Research Ethics Board and parental consents were waived. All term newborns (>36 weeks' gestation) with clinically suspected hypoxic ischemic encephalopathy were eligible if they were admitted to the Neonatal Intensive Care Unit of the British Columbia Children's Hospital and Women's Health Center, a provincial tertiary level neonatal center, between July 1, 2004, and September 30, 2012.[16,17] Hypoxic ischemic encephalopathy was defined as recognizable neonatal encephalopathy in the context of at least 1 of the following: (1) fetal distress at delivery, (2) Apgar score of ≤ 5 at 5 minutes, (3) requirement for resuscitation at birth, or (4) metabolic acidosis (umbilical artery pH <7.1 or base excess >10). Exclusion criteria included evidence of congenital infection, brain malformation or malformation of other major organs, neonatal stroke, or genetic syndrome including inborn errors of metabolism.

Therapeutic hypothermia was available in our neonatal intensive care unit prior to 2004 and has been the standard care since 2008. Term infants with moderate or severe neonatal encephalopathy underwent therapeutic hypothermia if they presented within 8 hours of life (2004-2007) or within 6 hours of life (2008-2012) and had 1 or more indicators of acute peripartum hypoxic ischemic insult, and clinical or amplitude-integrated electroencephalographic (aEEG) evidence of encephalopathy.[14,15] Total body cooling was initiated to 33–34°C and continued for 72 hours.

Clinical Data

Clinical information, including demographics, use of therapeutic hypothermia, occurrence of neonatal seizures, neurodevelopmental outcome, and incidence of childhood epilepsy, was collected by systematic chart review.

All glucose measurements up to 12 hours before the MRI study were recorded. Clinical hypoglycemia was defined as <2.6 mmol/L and severe hypoglycemia as <1.5 mmol/l.[14] A Neonatal Resuscitation Score was recorded ranging from 0 (no intervention) to 5 (endotracheal intubation with positive pressure ventilation and medication).[18] The degree of neonatal encephalopathy in the first 3 days of life was determined according to a modified Sarnat classification.[19] A neonatal encephalopathy score (range: 0-7) was calculated for each newborn, assigning 1 point for each abnormality in feeding, alertness, tone, respiratory status, and reflexes, and 2 points for clinical seizures.[20] A 5-point Neuromotor score was determined on the 1st, 3rd, and 10th days of life.[21]

Seizures and EEG Data

Clinical seizures (events identified by the attending physician as seizures and treated with antiepileptic medications) and electrographic seizures on aEEG or standard EEG were identified by chart review. The definition of clinical seizure we used was recurrent, rhythmical and nonsuppressible abnormal movements. The aEEG was monitored by neonatologists, NICU bedside nurses and/or neonatal neurologists. The aEEG results were collected by chart review because the original trace was not available. A neonatal seizure score from 0 to 10 was assigned based on the timing of seizure onset, seizure frequency, initial EEG findings, and need for antiepileptic therapy.[22] Status epilepticus was defined by the neurophysiologist based on conventional EEG when seizures comprised >30 minutes of any 60-minute EEG recording.

Conventional EEGs were performed based on clinical indications within 72 hours after birth. Each EEG trace was read by an EEG technician and a neurophysiologist with EEG certificate. The EEG technician codes EEG based on the EEG coding system and a neurophysiologist finalizes the report. All EEGs were graded by a neurophysiologist retrospectively using both the codes and EEG reports. If the technician's code was not consistent with the EEG report, or there was incomplete information to grade the tracing, the original EEG trace was reviewed in full. EEG results were interpreted systematically by a neurophysiologist, with particular attention to background patterns for age. EEGs were graded as 1 to 5; 1 (normal) and 5 (severely abnormal), based on the continuity of background activity particularly during quiet sleep, bihemispheric synchrony, background amplitude, symmetry, and degree of dysrhythmia.[22]

The treatment protocol for neonatal seizures at our center is as follows: phenobarbital 20 mg/kg loading dose is followed by additional doses up to a total 40 mg/kg if seizures persist. If seizures remain uncontrolled, intravenous phenytoin, midazolam or levetiracetam are given subsequently under the guidance of a neonatal neurologist. If seizures are controlled after the initial loading dose infants are usually treated with maintenance phenobarbital 5-6 mg/kg/day as guided by the phenobarbital blood level.

MRI Studies

Standardized MR imaging was performed between days 3 and 5 of life, after infants were rewarmed after therapeutic hypothermia with sedation on a Siemens 1.5 Tesla Avanto using VB 16 software, according to a previously published protocol.[23] The following sequences were obtained (time of relaxation/time of echo/averages/field of view/thickness/gap): axial and coronal T_1-weighted spin echo images (800/20/1/230/4 mm/0.2 mm), axial fast spin echo T_2-weighted images (4000/101/2/230/4 mm/0.5 mm), and isotropic diffusion weighted imaging $b = 700$, 1000 (3300/82/4/210/4 mm/ 0.2 mm). Both diffusion weighted imaging images and apparent diffusion coefficient maps were produced.

MR scans were reviewed by a pediatric neuroradiologist, blinded to clinical history and who scored the patterns and extent of lesions, as previously published (intraobserver reliability: >0.9).[10,15,23] The T_1- and T_2-weighted images as well as diffusion weighted imaging and apparent diffusion coefficient maps were reviewed and scored in accordance with a modified scoring system of Barkovich.[21,23] The

extent of injury on each sequence was scored from 0 to 4 in deep gray matter and from 0 to 5 in watershed region. The maximal score was assigned to 5 predominant patterns of injury, as follows: Normal, Watershed (injury in watershed region higher than the basal nuclei), Basal Nuclei (injury in the basal nuclei equal to or higher than watershed injury), Total (maximal injury in basal nuclei and watershed region), Focal-Multifocal (focal and multifocal white matter lesions and stroke).[23] The imaging features of neonatal hypoglycemia include abnormal signal in the posterior white matter, optic radiations and pulvinar.[14,15] The extent of injury to motor cortex and occipital cortex were scored from 0 to 3: 0 = normal; 1 = minimal involvement—restricted diffusion with focal or multifocal involvement of <25% of the cortex; 2 = moderate involvement—restricted diffusion in 25-50% of the cortex; and 3 = severe involvement—restricted diffusion in >50% of the cortex. Hippocampal injury was scored as (1) present, (0) absent.

Outcome Measures

Neurodevelopmental follow-up was assessed by a pediatric neurologist or pediatrician. Epilepsy was diagnosed based on clinical and EEG features and was defined as recurrent, unprovoked seizures, or a single seizure with abnormal EEG and initiation of medication. Cerebral palsy was defined according to the standard definition.[24] Gross Motor Function Classification System was collected from the medical records or assigned retrospectively based on clinical features, and graded on a scale of 1 to 5 based on gross motor function, where 5 is the most severe.[25] Clinical information including history of G-tube feeding, aspiration pneumonia, hearing impairment, or cortical blindness was obtained.

Statistical Analysis

Statistical analysis was performed with Stata 11 software (Stata Corporation, College Station, TX). Descriptive statistics were used to characterize the cohort for childhood epilepsy and hypoxic ischemic brain injury. Fisher's exact test and Kruskal-Wallis analysis of variance were used for categorical and continuous variables respectively. Logistic regression was performed to examine the relationships between specific brain injury and epilepsy. A backward selection model was used to determine the clinical risk factors, anatomical lesions, and patterns of injury most associated with childhood epilepsy, sequentially removing variables with P values >.1.

Results

Clinical Data

From July 2004 to September 2012, 223 newborns with neonatal encephalopathy were identified: of these, 42 (19%) were excluded (Figure 1), leaving 181 (81%) with suspected hypoxic ischemic encephalopathy. Fifteen (8%) died in the 1st month of life. Of 166 survivors, 132 subjects (80%) had follow-up at our institution until April 30, 2017, 19 who were evaluated by community physicians and 15 were lost to follow-up. Within the study period (13 years), 4 children died between 10 months and 5 years of age. Of the 132 children assessed at our institution, the median age at last follow-up was 61 months (interquartile range [IQR]: 28–96 and the current living median age is 8.8 years old (IQR: 84–126 months).

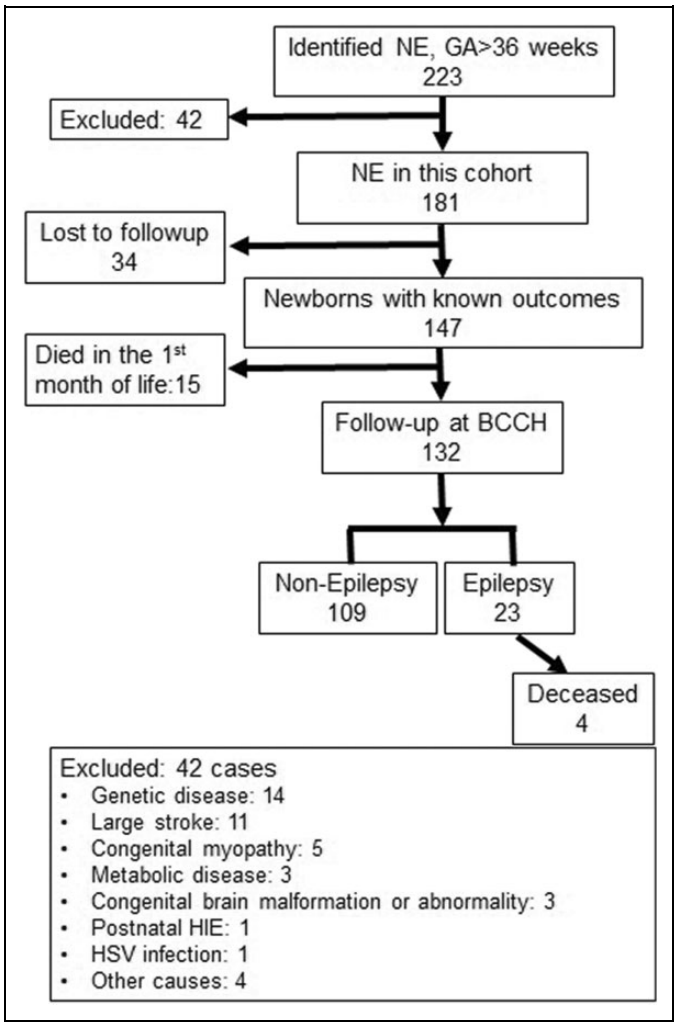

Figure 1. Flow Chart of the Study.

All 181 newborns had MRI performed between days 3-5 of life and 81 (45%) were rescanned on 10-14 day of life. Fifty-five infants (30%) received hypothermia therapy. Of the 126 infants who were not cooled; 41 (32%) presented after the cutoff window, 16 (12%) had contraindications, 50 (39%) did not meet the criteria for cooling, and 20 (16%) were not cooled for unknown reasons. Prior to 2008, there were 93 infants in this cohort, 41 (44%) were cooled and 52 (56%) not cooled.

Infants with follow-up at our institution were "sicker" than those with no follow-up. They had higher Sarnat score at admission ($P = .0005$) and 72 hours ($P = .0001$), higher Encephalopathy score on day 1 and 3 ($P = .005$ and $P = .0004$), and higher percentage of neonatal seizures ($P = .001$). The rate of therapeutic hypothermia was similar between the 2 groups ($P = 1.0$).

Perinatal Risk Factors for Epilepsy

Clinical demographic variables are summarized in Table 1. Of 132 subjects (80%) had follow-up at our institution until April 30, 2017, 23 (17%) were diagnosed with epilepsy. Children with and without childhood epilepsy did not differ in terms

Table 1. Clinical Characteristics and Neurodevelopmental Outcomes of the 147 Children With Hypoxic-Ischemic Encephalopathy.

Clinical characteristics	Epilepsy (N = 23)	No epilepsy (N = 124)	*P* value
Male, n (%)	14 (61)	77 (62)	>.9
Gestational age at birth, median weeks (IQR)	39.5 (38–40)	39.5 (38–40)	.30
Birth weight, median grams (IQR)	3221 (2779 – 3592)	3314 (2972 – 3697)	.26
Placental abruption, n (%)	7 (30)	14 (11)	.02
Chorioamnionitis, n (%)	2 (9)	13 (11)	>.9
Maternal group B streptococcus positive, n (%)	4 (23)	35 (34)	.57
Gestational DM, n (%)	4 (17)	15 (12)	.49
Apgar at 1 minute, median (IQR)	1 (1-3)	2 (1-3)	.07
Apgar at 5 minutes, median (IQR)	3.5 (3-7)	5 (3-6)	.38
Cord pH, median units (IQR)	7.0 (6.8-7.1)	7.0 (6.9-7.2)	.55
Birth meconium aspiration, n (%)	2 (10)	18 (15)	.74
Endotracheal intubation, n (%)	16 (69)	66 (53)	.17
Endotracheal intubation, median days (IQR)	4.5 (4-6)	2 (1-5)	.01
Neonatal resuscitation score, median (IQR)	4 (3-5)	4 (3-4)	.038
Cardiorespiratory resuscitation at birth, n (%)	12 (52)	33 (27)	.025
Clinical hypoglycemia, n (%)	7 (32)	27 (22)	.41
Lowest glucose level, (mmol/L) median (IQR)	2.8 (1.7-3.6)	3.2 (2.2-4.1)	.28
Initial Sarnat score, median (IQR)	2 (2-3)	2 (1-2)	.005
Neuromotor score day 1, median (IQR)	3 (3-3)	3 (2-3)	.04
Neuromotor score day 10, median (IQR)	3 (3-3)	3 (1-3)	.03
Encephalopathy day 1, median (IQR)	7 (7-7)	7 (5-7)	.007
Encephalopathy day 3, median (IQR)	5 (5-7)	4 (3-5)	.001
Neonatal seizure, n (%)	23 (100)	86 (69)	.001
Neonatal seizure score, median (IQR)	5 (4-6)	4 (0-4.5)	.0001
Neonatal seizure frequency (>1), n (%)	23 (100)	72 (84)	.06
Therapeutic hypothermia, n (%)	7 (30)	38 (30)	>.9
Neurodevelopmental outcome			
Age at last assessment (months), median (IQR)	98 (62-120)	50 (26-86)	.001
Cerebral palsy, n (%)	17 (74)	11 (13)	<.001
GMFCS, median score (IQR)	3.5 (0–5)	0 (0–1)	.0001
Abnormal neurodevelopment, n (%)	19 (83)	22 (25)	<.001
Neuromotor score at last follow-up, median (IQR)	5 (0–5)	0 (0–3)	<.001
G-tube feeding, n (%)	11 (58)	3 (4)	<.001
Aspiration pneumonia, n (%)	8 (47)	3 (4)	<.001
Hearing impairment, n (%)	7 (50)	6 (8)	<.001
Cortical blindness, n (%)	9 (53)	3 (4)	<.001

Abbreviations: GMFCS, Gross Motor Function Classification System; IQR, interquartile range; n, number of cases.

of gender, birth weight, or in utero exposure to illicit drugs or tobacco or maternal use of selective serotonin reuptake inhibitors. Treatment with therapeutic hypothermia was also similar between the 2 groups ($P > .9$). Neonates who developed childhood epilepsy required more resuscitation at birth and more support during the newborn period and had more severe encephalopathy (Table 1).

Neonatal Seizures and Risk of Epilepsy

Of the total 181 infants, 155 (86%) had conventional EEG performed in the first 3 days of life and 128 (70%) had clinical and/or electrographic neonatal seizures. Of these 128 newborns with neonatal seizures, 22 newborns (17%) had seizures confirmed on EEG/aEEG including 13 had EEG confirmed seizures with clinical signs and 9 only had electrographic seizures, and the seizures of the remaining 106 newborns were diagnosed based on clinical signs. Nineteen (15%) had a single recognized seizure, 107 (84%) had multiple seizures, and 2 (1.5%) had status epilepticus on EEG. Fourteen (8%) newborns required 3 or more antiseizure medications. Of the 128 newborns with neonatal seizures, 110 (86%) had their initial seizures during the first day of life. Of the 23 children who developed childhood epilepsy, all had more than 1 neonatal seizure, 5 (22%) had seizures confirmed on EEGs/aEEG with clinical signs, and 2 (9%) had status epilepticus on neonatal EEGs. Among these 23 newborns, 5 (22%) newborns were treated with 3 or more AEDs, 6 (26%) with 2 AEDs, 10 (43%) with 1 AED, and 2 (9%) newborns did not require any AEDs.

Brain Injury Associated With Neonatal Seizures and Epilepsy

In this cohort, the predominant pattern of hypoxic ischemic brain injury was strongly associated with neonatal seizures and

Table 2. Pattern of Brain Injury on Day 3 MRI in the Newborns With and Without Epilepsy.

Pattern of brain injury	Died <1 month old (n = 15)	Epilepsy (n = 23)	No epilepsy (n = 109)	*P* value
Predominant pattern				
Normal, n (%)	1 (7)	1 (4)	65 (60)	<.001
Watershed, n (%)	3 (20)	5 (22)	11 (10)	
Basal Nuclei, n (%)	6 (40)	10 (43)	13 (12)	
Total, n (%)	4 (27)	5 (22)	2 (2)	
Focal-Multifocal, n (%)	1 (7)	2 (9)	18 (17)	
Signal abnormalities in specific brain structures				
Hippocampus, n (%)	8 (53)	11 (48)	2 (2)	<.001
Motor cortex, n (%)	9 (60)	13 (59)	14 (13)	<.001
Occipital cortex, n (%)	9 (60)	10 (45)	13 (12)	.009

Abbreviations: IQR, interquartile range; n, number of cases.

childhood epilepsy (Table 2 and Figure 2). The 36 infants with injury to motor cortex were classified as mild (15 newborns; 42%), moderate (9; 25%), and severe (12; 19%). Evidence of MRI abnormality consistent with hypoglycemic injury occurred in 37 newborns (20%). In the 32 neonates with occipital injury, 38% (12 newborns) had mild, 25% (8) moderate, and 38% (12) severe injury.

Neonatal Seizures

Neonates with seizures did not differ in terms of gender, birth weight, maternal gestational diabetes, mode of delivery, birth complication (eg, placenta abruption, prolapsed cord, meconium aspiration), Apgar scores, neonatal resuscitation score (including CPR and/or ventilation), or tube feeding. Neonatal seizures were associated with higher Sarnat, neonatal motor and encephalopathy scores. (see Table 1)

Of the 128 neonates with neonatal seizures, 51 (40%) had normal MRI and 77 (60%) had abnormal MRI with patterns of injury as follows: Watershed, 20 (16%); Basal Nuclei, 30 (23%); Total, 10 (8%); and Focal-Multifocal, 17 (13%). Neonatal seizures were significantly associated with the predominant pattern of hypoxic ischemic injury ($P < .001$), MRI abnormality consistent with hypoglycemia (25% vs 9%, odds ratio = 3.2, 95% CI [1.2, 8.7], $P = .02$), and occipital injury (24% vs 2%, odds ratio = 3.2, 95% CI [1.2, 8.1], $P = .02$). Neonatal seizures were not associated with clinical hypoglycemia (23% vs 19%, odds ratio = 1.3, 95% CI [0.6, 2.8], $P = .57$) or hypothermia therapy (27% vs 32%, $P = .85$). However, using a logistic regression model adjusting for the predominant patterns of hypoxic ischemic injury, MRI changes following hypoglycemia, specific anatomic lesions on MRI and exposure to therapeutic hypothermia, the Basal Nuclei pattern was the

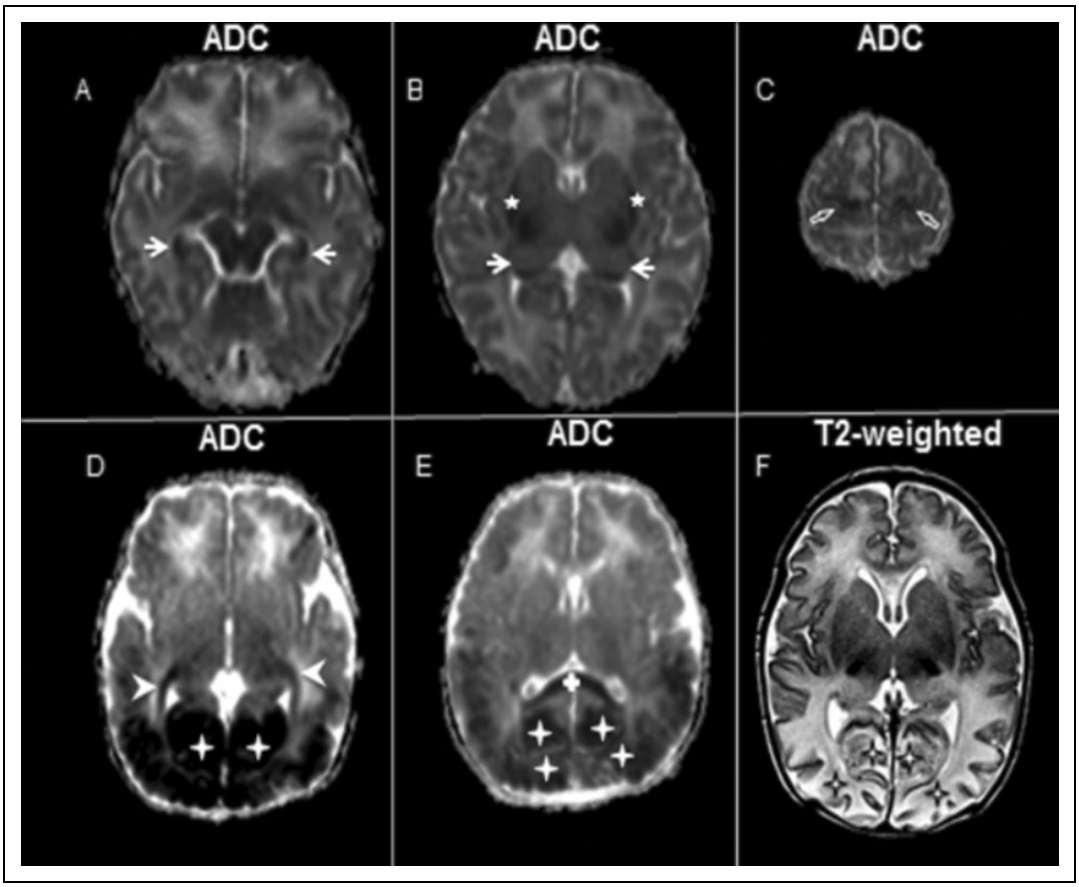

Figure 2. Signal Abnormalities on Brain Magnetic Resonance Scan on the Third Day of Life of Hypoxic-Ischemic Injury and Hypoglycemia Injury.

only independent risk factor for neonatal seizures (odds ratio = 8.6, 95% CI [1.5, 51.2], $P = .02$).

Neonatal EEG Findings

The EEG grading based on the degree of discontinuity, asynchrony, suppression and asymmetry and dysmaturity was not significantly different between the groups with and without subsequent childhood epilepsy ($P = .67$). However, EEG confirmed seizures with or without clinical signs were associated with development of childhood epilepsy (30% vs 9%, $P < .01$).

Brain injury and Childhood Epilepsy

In this cohort, there is a statistically significant association between childhood epilepsy and patterns of injury: Watershed (22%), Basal Nuclei (43%) and Total patterns of injury (22%), ($P < .001$). Injury to motor cortex (odds ratio = 6.3, 95% CI [2.4, 16.6], $P < .001$), hippocampi (odds ratio = 10.4, 95% CI [3.7, 29.6], $P < .001$), and occipital lobes (odds ratio = 3.8, 95% CI [1.5, 10.0], $P = .006$) were also risk factors for childhood epilepsy. When all 3 structures were included in the logistic model with adjustment for the predominant pattern of injury; Watershed (odds ratio = 16.0, 95% CI [1.3, 197.2], $P = .03$)) and Basal Nuclei (odds ratio = 19.4, 95% CI [1.9, 196.3], $P = .01$) remained independent risk factors for epilepsy. MRI abnormality consistent with hypoglycemic injury was not predictive of childhood epilepsy (odds ratio = 2.2, 95% CI [0.8, 5.7], P = 1.1). (Table 2)

In this cohort, 55 newborns (30%) were treated with hypothermia. Hypothermia therapy group didn't show decreased risk of developing childhood epilepsy ($P > .9$), even when accounting for brain injury on MRI (pattern and specific anatomical injuries) in a logistic regression model.

When the clinical risk factors, such as Apgar scores, Sarnat encephalopathy scores, intubation, and neonatal resuscitation were included in the logistic model with the predominant pattern of injury and all 3 structural lesions, the Basal Nuclei (odds ratio = 26.0, 95% CI [1.6, 415.7], $P = .02$) and Total injury pattern (odds ratio = 126.3, 95% CI [2.1, 7442.8], $P = .02$) remained as risk factors for epilepsy.

Epilepsy and Outcomes

Of the 23 children with epilepsy, 7 (30%) developed epileptic spasms: 6 developed spasms in the first year of life and 1 at 3.5 years old. The mean age of onset of unprovoked seizures (excluding epileptic spasms) was 31 months (range: 1 month to 7 years, 95% CI [16.2, 46.2]). There were 4 children (18%) who died in later age and they all had epilepsy: 1 (at age 5 years) died of cardiac arrest and another child (age 17 months) with chronic lung disease died of respiratory failure, and the other 2 children (aged 4 and 7 years) died of unknown causes. In the remaining 19 children, 17 (90%) were well controlled (more than 1-year seizure free) with 0-2 antiseizure medications, 1 (5%) had treatment resistant epilepsy and 1 child recently developed epilepsy and had not yet started antiseizure therapy.

Most infants (19, 83%) with childhood epilepsy had abnormal neurodevelopment including cerebral palsy, G-tube feeding, aspiration pneumonia, hearing impairment, and cortical visual impairment (Table 1, Table 2, and Table 3).

Discussion

In this retrospective cohort of term newborns with neonatal encephalopathy, all neonates had standardized neonatal MRI in the first 3-5 days of life and were followed up to early school age (median age at last follow-up: 61 months old). In the context of the evolving nature of hypoxic ischemic over time, the uniformity of MR timing is of particular importance. In term newborns with hypoxic ischemic encephalopathy, the predominant pattern of brain injury on MRI is robustly detectable between 3 and 5 days of life.[23,26] All children in our study had MRI imaging during this time frame. Our data indicate that Watershed and Basal Nuclei patterns of hypoxic ischemic injury are independent predictors of childhood epilepsy (odds ratio = 16.0 and 19.4, respectively, all $P < .05$) and that a clear relationship exists between lesions in the motor cortex, hippocampus and occipital cortex and childhood epilepsy (odds ratio = 6.3, 10.4, and 3.8, all $P < .05$, respectively). In contrast, MRI abnormality consistent with hypoglycemic injury increased the risk of neonatal seizures (odds ratio = 3.2, $P < .05$) but was not predictive of later epilepsy (odds ratio = 2.2, $P = 1.1$). These findings are also in agreement with previous studies which suggest increased risk of epilepsy in children who had a moderate-severe spectrum of hypoxic ischemic and/or recurrent neonatal seizures.[6,7,12,27] In term of the generalizability of our findings, the 17% prevalence of epilepsy in our cohort is similar to that reported previously.[6,7,9,10,27]

The pathophysiological mechanisms that mediate epileptogenesis following hypoxic ischemic encephalopathy are poorly understood. Animal studies indicate that direct injury to cortical pyramidal neuron in the developing brain and subsequent cortical hypertrophy to compensate for neuronal loss as well as synaptic reorganization of thalamocortical, callosal, dentate gyrus, and intracortical circuitry, and failure to prune immature connections all likely contribute to hyperinnervated circuitries, which are the basis of epileptogenesis.[28,29] Furthermore, recurrent neonatal seizures may result in increased excitability in the neuronal network of the neocortex.[30] We postulate that the mechanism of increased risk of childhood epilepsy after moderate and severe perinatal hypoxic ischemic injury is multifactorial; the acute hypoxic ischemic brain injury, particularly the Watershed and Basal Nuclei patterns, and other acquired injury such as injury secondary to neonatal seizures cause damage to neurons predominantly in the motor cortex, occipital cortex, hippocampus, and deep gray nuclei. The subsequent growth of neurons and chronic synaptic reorganization form abnormal hyperinnervated circuitry between cortical neurons and/or form abnormal cortical-deep neuronal networks. These abnormal

Table 3. Characters of Study Subjects With Childhood Epilepsy (23 Cases).

	Epilepsy				Neonatal evaluation			Outcome	
Age, gender	Type of seizures (onset)	Seizure control	Current AED	AED tried	Neonatal seizure descriptions	EEG findings in newborn	MRI pattern of injury	Cerebral palsy (types/GMFCS)	Neurodevelopmental deficits
Died (7 yr), M	Focal motor (9 mo)	Well controlled before died	Clonazepam	Clonazepam	Autonomic features, eyes deviation, focal clonic, lip smack	Severe suppression, frequent sharp waves, bilateral temporal sharp	Basal Nuclei	Spastic quadriparesis, IV	Motor, language, cortical blindness, G-tube fed, aspiration pneumonia
Died (1 yr), M	Infantile spasms (2 mo) and focal motor (3 mo)	Died	None	Vigabatrin, nitrazepam, levetiracetam, topiramate	Not available		Total	Spastic quadriparesis, V	Motor, language, hearing, cortical blindness, G-tube fed, aspiration pneumonia
12 yr, M	Focal (1 mo)	Well controlled	Phenobarbital	Phenobarbital	Eyes deviation, multifocal clonic movements	Moderate discontinuity and suppression, midcentral electrographic seizure	Basal Nuclei	Spastic quadriparesis, Choreoathetotic, V	Motor, language, cortical blindness, G-tube fed, aspiration pneumonia
5 yr, F	Focal motor (13 mo)	Well controlled	Clobazam	Clobazam	Focal clonic, multifocal clonic movements	Mid-discontinuity and suppression, slow background, multifocal sharps	Watershed	Hemiplegia, I	Motor
8 yr, F	Infantile spasms (7 mo) and focal motor (4 mo)	Well controlled, seizure free >5 years	Nitrazepam, topiramate	Nitrazepam, topiramate	Apnea, clonic movement	Severe suppression	Total	Spastic quadriparesis, V	Motor, language, hearing, cortical blindness, G-tube fed, aspiration pneumonia
8 yr, M	Infantile spasms (4 mo), focal (1 mo)	Refractory	Nitrazepam levetiracetam	Carbamazepine, nitrazepam, valproic acid, vigabatrin, ACTH, phenobarbital	Tonic movement of limbs	Severe suppression, left occipital electrographic seizures	Basal Nuclei	Choreoathetotic, IV	Motor, language delay, cortical blindness, aspiration pneumonia
Died (4 yr), F	Infantile spasms (3 mo) and focal (1 mo)	Well controlled	Nitrazepam	Nitrazepam, vigabatrin, ACTH, levetiracetam, VNS	Apnea, cycling	Severe discontinuity suppression, asynchrony, left occipital electrographic seizure	Total	Spastic quadriparesis, V	Motor, language, hearing, cortical blindness, G-tube fed

(continued)

Table 3. (continued)

	Epilepsy				Neonatal evaluation			Outcome	
Age, gender	Type of seizures (onset)	Seizure control	Current AED	AED tried	Neonatal seizure descriptions	EEG findings in newborn	MRI pattern of injury	Cerebral palsy (types/GMFCS)	Neurodevelopmental deficits
9 yr, F	Focal motor (70 mo)	Well controlled	None	Clobazam	Focal clonic, myoclonic jerking	Moderate discontinuity and suppression	Watershed	No	No
Died (17 mo), M	Infantile spasms (4 mo) and focal motor (4 mo)	Died		Topiramate, nitrazepam, phenobarbital, phenytoin	subclinical seizure	Severe discontinuity, severe suppression, bilateral occipital electrographic seizures	Total	Spastic quadriparesis, V	Motor, language, cortical blindness, G-tube fed, aspiration pneumonia
12 yr, M	Focal motor (2.5 yr), atypical absence	Well controlled	Lamotrigine	Topiramate, valproic acid, lamotrigine	Apnea, autonomic features, lip smack	Mod discontinuity suppression, frequent sharp	Normal	No	Motor, language, hearing
6 yr, F	Focal motor (13 mo)	Well controlled	None	Clobazam	Focal clonic, lip smack	Mod suppression	Focal-Multifocal	No	Normal
5 yr, F	Focal (2 mo)	Well controlled	None	Clobazam	Eyes deviation, eye flutter	Severe suppression	Basal Nuclei	Spastic quadriparesis, dystonic, choreoathetotic, II	Gross/fine motor, language, G-tube fed
11 yr, F	Infantile spasms (4 mo) then focal motor (7 yr)	Well controlled	None	Vigabatrin, flunarizine	Eyes deviation, myoclonic jerking	Moderate discontinuity, suppression, asynchrony, frequent multifocal sharps	Basal Nuclei	Spastic quadriparesis, choreoathetotic, III	Gross/fine motor, language
12 yr, M	Focal motor (9 yr)	Well controlled	Clobazam	Clobazam, phenobarbital	Electrical seizures	Moderate suppression, asynchrony, multifocal spikes	Total	Spastic quadriparesis, I	Gross/fine motor, language
8 yr, F	Focal (6 mo), epileptic spasm (3.5 yr)	Refractory, daily	CBD oil	Lamotrigine, levetiracetam phenobarbital, vigabatrin, valproic acid, carbamazepine	Focal tonic-clonic movement	Electrographic seizures in right parietal central and left temporal area	Watershed	No	Gross/fine motor, language, cortical blindness
5 yr, F	Unknown	Well controlled	None	Clonazepam	Myoclonic jerking	Mild suppression	Basal Nuclei	Hypotonic, V	Gross/fine motor, language, hearing

(continued)

Table 3. (continued)

	Epilepsy				Neonatal evaluation			Outcome	
Age, gender	Type of seizures (onset)	Seizure control	Current AED	AED tried	Neonatal seizure descriptions	EEG findings in newborn	MRI pattern of injury	Cerebral palsy (types/GMFCS)	Neurodevelopmental deficits
10 yr, M	Focal (2 yr)	Well controlled	Lamotrigine	Lamotrigine, topiramate, carbamazepine, clobazam	Myoclonic jerking	Moderate discontinuity, suppression, mild asynchronous, multifocal spikes	Basal Nuclei	Spastic quadriparesis, dystonic, II	Gross/fine motor, language, hearing
6 yr, M	Focal (5 yr)	Well controlled	Clobazam		Cycling	Severe discontinuity	Focal-Multifocal	No	Gross/fine motor, language
8 yr, M	Focal (4 yr)	Well controlled	Clobazam	Clobazam, phenobarbital	Autonomic, cycling, focal clonic, myoclonic	Severe suppression, multifocal sharp	Watershed	Hemiplegia, IV	Language
12 yr, F	Focal (2 yr)	Well controlled	Topiramate, levetiracetam clobazam	Phenobarbital, topiramate, levetiracetam	Autonomic features, lip smacking, tonic	Moderate suppression	Basal Nuclei	Spastic quadriparesis, V	Gross/fine motor, language, hearing impairment
5 yr, F	Focal (2 yr)	Well controlled	Levetiracetam	Levetiracetam, Phenobarbital	Electrographic seizures	Moderate suppression, asynchrony, multifocal spikes	Basal Nuclei, hypoglycemia features	Spastic quadriparesis, V	Gross/fine motor, language, cortical blindness, G-tube fed, aspiration pneumonia
9 yr, F	Focal (8 yr)	Well controlled	Lamotrigine		Focal clonic, myoclonic jerking, SE	Mild suppression, moderate discontinuity, asynchrony	Watershed	No	Motor, language, hearing, G-tube fed
4 yr, M	Focal motor (4.5 yr)	New diagnosis, parents not willing treat			Apnea, Autonomic features, Eyes deviation, posture	Discontinuity, moderately suppressed	Basal Nuclei	Spastic quadriparesis, IV	Gross/fine motor, language, G-tube fed, aspiration pneumonia

Abbreviations: ACTH, adrenocorticotropic hormone; AED, antiepileptic drug; EEG, electroencephalogram; F, female; GMFCS, Gross Motor Function Classification System; M, male; mo, months; NICU, neonatal intensive care unit; SE, status epilepticus; VNS, vagal nerve stimulator; yr, years.

networks with high excitability mediate epileptogenic foci at a later age.

The ability to determine specific anatomical patterns of neonatal brain injury that are more likely associated with development of later childhood epilepsy is highly relevant clinically to determine a need for follow-up and to provide accurate prognostic counselling. In neonates, the presence, frequency and duration of seizure activity may contribute to additional brain injury, which further increases the risk of subsequent neurodevelopmental impairment and epilepsy.[16,30] However, treatment strategies for neonatal seizures may be toxic to the developing brain.[31] Furthermore, antiepileptic drugs such as phenobarbital have been associated with depressed cognitive function.[32] On the other hand, both neonatal seizures and antiseizure medications contribute to parental worries and have major impact on families.[33] Our data suggest that newborns with Watershed, Basal Nuclei, or Total injury, especially if the hippocampus, motor, or occipital cortex are involved, warrant close monitoring for future need for antiseizure therapy.

Although our findings do not support reduced risk for epilepsy in cooled infants,[12] these data do not exclude this possibility. Therapeutic hypothermia has been shown to reduce death and disability in several randomized, controlled trials,[4,34] and reduce the risk of the development of epilepsy in newborns with perinatal hypoxic ischemic encephalopathy.[27] In this study, only 30% of newborns with hypoxic ischemic injury received hypothermia therapy. Infants who underwent therapeutic hypothermia were significantly sicker at birth and required more invasive therapeutic interventions. Despite these differences, the risk of developing long-term epilepsy was similar in cooled and noncooled infants. In other words, that the risk of epilepsy was not increased in sicker newborns as might be expected suggests that therapeutic hypothermia may be protective.

There are some limitations to this study, which should be acknowledged. Due to the retrospective nature of this study, among the 181 infants in the cohort, the loss to follow-up rate was 20% (34 infants, although 56% of these were followed by the community physicians). This may have resulted in an overestimation of the prevalence of epilepsy because children lost to follow-up were generally healthier with milder encephalopathy and less severe brain injury. On the other hand, of children who had follow-up, 12.5% (16 infants) were younger than 12 months of age at the last visit, which might have resulted in underestimation of the prevalence of epilepsy. Unless children without follow-up moved to another province, it is unlikely that their epilepsy went undocumented given that our center is the only institution which provides tertiary-level pediatric neurology in the province. Another limitation relates to the lack of neonatal continuous EEG monitoring which may contribute to the low incidence of status epilepticus in this cohort.

In summary, neonatal hypoxic ischemic encephalopathy is an important cause of acquired neonatal brain injury with significant risk for adverse long-term outcome including childhood epilepsy. In contrast, neonatal hypoglycemia with MRI abnormalities may be less predictive of later epilepsy. Evidence of injury on neonatal MRI specifically to Basal Nuclei and Watershed regions and injury to hippocampi, motor, and occipital cortices are associated with increased risk of childhood epilepsy. These data assist in the early identification of newborns at increased risk for seizures and who may require ongoing monitoring for epilepsy in later childhood. Future studies are required to determine optimal therapy for newborns who are at high risk for subsequent epilepsy as well as the potential beneficial effect of therapeutic hypothermia on reduction of childhood epilepsy.

Author Contributions

Qi Xu contributed to study design, collected and analyzed the clinical data, reviewed the literature. She drafted and revised the manuscript. Vann Chau contributed to study design and provided important guidance to the study. He helped to analyze the clinical data, critically revised the manuscript and gave the final approval. Chinnuwat Sanguansermsri was involved in collecting and analyzing EEG data as an epilepsy fellow. He reviewed the manuscript for important intellectual content. Katherine E. Muir collected clinical data and reviewed the manuscript for important intellectual content. Emily W. Y. Tam provided important clinical guidance and reviewed the manuscript for important intellectual content. Steven P. Miller provided important guidance to study design and critically revised the manuscript. Darren S. T. Wong collected clinical data and neuroimaging data and reviewed the manuscript for important intellectual content. Hao Chen provided statistical support to data analysis as a statistician. Peter K. H. Wong provided important guidance to analyze EEG data and reviewed manuscript. Jill G. Zwicker contributed to study design, reviewed the manuscript for important intellectual content. Kenneth J. Poskitt contributed to study design. He reviewed and analyzed all MRI scan data. He critically revised the manuscript. Alan Hill contributed to study design, provided important guidance to the study. Elke H. Roland contributed to study design, provided important guidance to the study. She reviewed and critically revised the manuscript.

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Ethical Approval

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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