



Research Paper

Disorders of Neuronal Migration/Organization Convey the Highest Risk of Neonatal Onset Epilepsy Compared With Other Congenital Brain Malformations



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ARTICLE INFO

Article history:

Received 12 July 2021

Accepted 6 November 2021

Available online 12 November 2021

Keywords:

Neonatal seizures

EEG

Electroencephalogram

Epilepsy

Neurocritical care

Neonatal encephalopathy

Congenital abnormalities

Seizure

Antiseizure medication (ASM)

ABSTRACT

Background: Although seizures in neonates are common and often due to acute brain injury, 10–15% are unprovoked from congenital brain malformations. A better understanding of the risk of neonatal-onset epilepsy by the type of brain malformation is essential for counseling and monitoring.

Methods: In this retrospective cohort study, we evaluated 132 neonates with congenital brain malformations and their risk of neonatal-onset epilepsy. Malformations were classified into one of five categories based on imaging patterns on prenatal or postnatal imaging. Infants were monitored with continuous video EEG (cEEG) for encephalopathy and paroxysmal events in addition to abnormal neuroimaging.

Results: Seventy-four of 132 (56%) neonates underwent EEG monitoring, and 18 of 132 (14%) were diagnosed with neonatal-onset epilepsy. The highest prevalence of epilepsy was in neonates with disorders of neuronal migration/organization (9/34, 26%; 95% confidence interval [CI] = 13–44%), followed by disorders of early prosencephalic development (6/38, 16%; 95% CI = 6–31%), complex total brain malformations (2/16, 13%; 95% CI = 2–38%), and disorders of midbrain/hindbrain malformations (1/30, 3%; 95% CI = 0–17%). Of neonates with epilepsy, 5 of 18 (28%) had only electrographic seizures, 13 of 18 (72%) required treatment with two or more antiseizure medicines (ASMs), and 7 of 18 (39%) died within the neonatal period.

Conclusion: Our results demonstrate that disorders of neuronal migration/organization represent the highest-risk group for early-onset epilepsy. Seizures are frequently electrographic only, require treatment with multiple ASMs, and portend a high mortality rate. These results support American Clinical Neurophysiology Society recommendations for EEG monitoring during the neonatal period for infants with congenital brain malformations.

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Conflict of interest: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Hannah C. Glass, MDCM, MAS received funding from PCORI, NIH, and Cerebral Palsy Alliance during the course of this study. She has received payment for legal consulting. Adam Numis, MD, reported grants from the National Institute of Neurological Disorders and Stroke (NINDS) (K23NS105918) and payments for expert testimony for medicolegal consulting outside the submitted work. Dawn Gano, MD, MAS, reported grants from the UCSF California Preterm Birth Initiative funded by Marc and Lynne Benioff and Cerebral Palsy Alliance and payment for medicolegal consulting. The remaining authors have nothing to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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<https://doi.org/10.1016/j.pediatrneurol.2021.11.005>

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Introduction

Although seizures in neonates are common with an incidence of 1–3.5/1000,¹ the risk of neonatal-onset epilepsy related to particular brain malformations is not well understood. Most neonatal seizures are caused by hypoxic ischemic encephalopathy or other acute brain injuries; however, approximately 10–15% are unprovoked seizures due to early-onset epilepsy caused by a genetic epileptic encephalopathy or congenital brain malformation.^{2,3} Up to one-third of neonatal-onset epilepsies have a brain malformation as the underlying cause.³ Seizures are a common presenting feature in children with congenital brain malformations and often herald medically refractory epilepsy.⁴

Although congenital brain malformations are a recognized risk factor for epilepsy, less is known about the neonatal incidence and age of onset for various brain malformations. A genetic diagnosis is rarely available to guide management at birth; therefore, clinicians must rely on imaging patterns to classify the malformation and determine risk of early-onset epilepsy. Epileptogenesis in the setting of congenital brain malformations has been explained as an abnormality in the excitatory-to-inhibitory synaptic ratio, which can arise from multiple mechanisms including disrupted cell division, neuronal migration, development of the synaptic bouton, and dendritic morphogenesis.^{5–7} A better understanding of the relationship between risk of neonatal-onset epilepsy and type of brain malformation is essential for prenatal counseling and clinical decision-making regarding postnatal electroencephalogram (EEG) monitoring.

The 2011 American Clinical Neurophysiology Society (ACNS) guidelines recommend continuous EEG (cEEG) monitoring for 24 hours in high-risk neonates, including those with cerebral dysgenesis.⁸ Little is known about how the guidelines are applied in clinical practice or the yield of neonatal monitoring in children with congenital brain malformations.

We identified neonates with prenatally or postnatally diagnosed congenital brain malformations, evaluated in a quaternary care hospital, to examine the prevalence of neonatal-onset epilepsy within different types of congenital brain malformations. We hypothesized that a higher rate of neonatal-onset epilepsy would be found in neonates with disorders of neuronal migration/organization and complex total brain malformations than brain malformations that did not primarily impact cortical development.

Methods

This was a retrospective cohort study of neonates who were admitted to the UCSF Benioff Children's Hospital Intensive Care Nursery (ICN) and were evaluated by the Neurointensive Care Nursery Neonatal Neurocritical Care Service for congenital brain malformations from 2008 to 2019. Infants were studied using a waiver of consent approved by the UCSF Institutional Review Board. Inclusion criteria were congenital brain malformations identified on prenatal or postnatal MRI and evaluation by a child neurologist during the neonatal period. Exclusion criteria were central nervous system malformations not known to cause epilepsy (i.e., isolated neural tube defects, isolated ventriculomegaly, isolated myelination abnormalities), and acute brain injury. Prematurity was defined as gestational age <37 weeks.

A child neurologist reviewed prenatal (fetal MRI obtained between 20 and 27 weeks' gestation) and postnatal imaging (MRI or head ultrasound) reports to classify malformations into one of five categories originally defined by Volpe⁹ as follows: (1) disorders of

early prosencephalic development, occurring during the second and third months of gestation including prosencephalic formation (anencephaly), cleavage (holoprosencephaly), and midline development (corpus callosum agenesis, septo-optic dysplasia),¹⁰ (2) congenital hydrocephalus, which can be associated with additional major central nervous system abnormalities in up to 70% of cases,^{11,12} (3) disorders of midbrain/hindbrain development, which can also be associated with migratory disorders of the cerebral cortex,^{13,14} (4) disorders of neuronal migration/organization, with peak occurrence between the third and fifth months of gestation,¹⁵ (5) complex total brain malformations (defined as malformations spanning two or more categories).¹⁶ Malformations were further subcategorized by developmental anomalies within a category as follows:

- (1) Disorders of early prosencephalic development
 - a. Corpus callosum hypoplasia/dysplasia
 - b. Complete corpus callosum agenesis
 - c. Septo-optic dysplasia
 - d. Holoprosencephaly
 - e. Anencephaly
- (2) Congenital hydrocephalus
- (3) Disorders of midbrain/hindbrain development
 - a. Cerebellar dysplasia/hypoplasia
 - b. Dandy-Walker malformation
 - c. Isolated cerebellar vermis hypoplasia
 - d. Joubert syndrome
 - e. Pontocerebellar hypoplasia
 - f. Rhombencephalosynapsis
- (4) Disorders of neuronal migration/organization
 - a. Polymicrogyria
 - b. Lissencephaly/pachygyria
 - c. Gyral simplification
 - d. Gray matter heterotopia
 - e. Frontal hypoplasia
 - f. Schizencephaly
- (5) Complex total brain malformations
 - a. Complex total brain malformations not otherwise specified
 - b. Tuberous sclerosis complex (TSC)
 - c. Aicardi syndrome
 - d. DiGeorge syndrome
 - e. L1CAM
 - f. Trisomy 18
 - g. Walker Warburg syndrome

Infants with multiple brain anomalies within a single brain malformation category were identified by the most prominent brain abnormality.

Clinical and demographic data were extracted from the clinical records by a trained clinical research coordinator. Local clinical guidelines during the study period recommended continuous video EEG monitoring for children with encephalopathy (defined as alterations in mental status, hypotonia, abnormalities in feeding or respiration, and seizures⁹), paroxysmal events (abnormal movements concerning for seizure or unexplained apneic events), or abnormal neuroimaging, including congenital brain malformations. Predominant EEG background, presence of abnormalities, and seizure semiology were determined by a child neurologist based on clinical records. Status epilepticus was defined as continuous seizure activity or recurrent seizures for more than 50% of 1–3 hours of recording time.¹⁷ While all infants in this study technically met

criteria for monitoring based on abnormal imaging, if they also displayed evidence of encephalopathy or paroxysmal events, those were considered the primary indication for cEEG. Timing and application of cEEG was at the discretion of the attending physician.

Seizures were identified by cEEG monitoring reviewed by experienced pediatric neurophysiologists in the clinical setting. EEG reports were reviewed by one of the authors who is epilepsy trained (R.S.), and seizures were classified according to the 2021 International League Against Epilepsy classification scheme of seizures in neonates.¹⁰ Neonatal-onset epilepsy was defined, in keeping with the International League Against Epilepsy definition of epilepsy,¹¹ as a disorder characterized by seizures (either electroclinical or electrographic only) identified before discharge from the intensive care nursery.

Analyses were performed using StataSE16 (Stata, College Station, TX) and Microsoft Excel (Redmond, WA). Binomial probability confidence intervals (CIs) were calculated using the Clopper-Pearson exact method.

Results

Between 2008 and 2019, 132 children met inclusion criteria. Neonates were admitted or transferred to the ICN for cardiopulmonary monitoring, respiratory, hemodynamic or feeding support, or specialized procedures including cEEG. Sixty-four of 132 were female (48%), and 5 of 132 (4%) were born premature (Table 1). The majority of neonates (84/132, 64%) were diagnosed with suspected congenital brain malformations by prenatal ultrasound or fetal MRI. Diagnosis was confirmed by postnatal imaging in 117 of 132 (89%). Reasons for not receiving postnatal MRI included being medically unstable or not aligning with parent goals of care. Seventy-four of 132 (56%) neonates underwent video EEG monitoring, and 18 of 132 (14%) were diagnosed with neonatal-onset epilepsy. Mortality was significantly higher for neonates diagnosed with epilepsy (7/18 [39%]) than for children who did not have seizures in the neonatal period (13/114 [11%], $P = 0.003$). Autopsy was performed in only one child; results were concordant with brain MRI findings of polymicrogyria.

Brain malformation classification and frequency of monitoring are presented in Table 2. Children with disorders of early prosencephalic development, disorders of neuronal migration/organization, and complex total brain malformations were more likely to receive cEEG monitoring than children with disorders of midbrain/hindbrain development and congenital hydrocephalus.

TABLE 1.
Clinical Characteristics, Diagnostic Evaluations, and Outcome for 132 Infants With Congenital Brain Malformations Evaluated for Early-Onset Epilepsy

Clinical Features	N = 132
Clinical Characteristic	
Female	64 (48%)
Premature (<37 weeks GA)	5 (4%)
Prenatal diagnosis	84 (64%)
Diagnostic Evaluation	
Fetal MRI	49 (37%)
Neonatal MRI	117 (89%)
Neonatal EEG	74 (56%)
Outcome	
Neonatal-onset epilepsy	18 (14%)
Neonatal death	20 (15%)

Abbreviations:

EEG = Electroencephalogram

GA = Gestational age

MRI = Magnetic resonance imaging

Data are presented as n (%).

Neonatal-onset epilepsy was diagnosed in 18 of 132 (14%, Table 3). The highest risk of epilepsy was among children with a disorder of neuronal migration/organization (9/34, 26%; 95% CI = 13–44%), followed by children with a disorder of early prosencephalic development (6/38, 16%; 95% CI = 6–31%), complex total brain malformation (2/16, 13%; 95% CI = 2–38%), and disorder of midbrain/hindbrain malformations (1/30, 3%; 95% CI = 0–17%) (Fig). Children with polymicrogyria accounted for 6 of 18 (33%) and lissencephaly/pachygyria for 3 of 18 (17%) of all children diagnosed with neonatal-onset epilepsy. Seizure onset was at a median of 2 days (interquartile range = 1, 2), excluding one premature infant with seizure onset at 60 days after birth, reflecting postmenstrual age of 38 weeks. There was no report of seizures in utero. Most children were monitored for a clinical indication of abnormal imaging (32/74 [43%]) or paroxysmal events concerning for seizures (29/74 [39%], Table 4).

Seventeen of 18 (94%) children with neonatal-onset epilepsy had an EEG report available for review, and of these, 16 of 17 (94%) were abnormal. EEG abnormalities included voltage attenuation, asynchrony, excess discontinuity, excess fast activity in the alpha/beta range, and epileptiform discharges (sharp waves and spikes). Among the 13 of 18 (72%) children with electroclinical seizures, seizure semiology was as follows: autonomic (5/13 [38%]), clonic (4/13 [31%]), tonic (2/13 [15%]), and myoclonic (2/13 [15%]). Five of 18 (28%) infants had only electrographic seizures, although 11 of 18 (61%) had seizures without clinical correlate at some point during the recording.

Thirteen of 18 (72%) infants were treated with two or more antiseizure medicines (ASMs) including phenobarbital, fosphenytoin, levetiracetam, topiramate, oxcarbazepine, and benzodiazepines (lorazepam and midazolam), administered as a combination of boluses, maintenance, or both (Table 3). There was no difference in use of two or more ASMs among neonates with epilepsy who died (5/7; 71%) as compared with neonates with epilepsy who did not die (8/11; 73%, $P = 0.95$).

Discussion

In a cohort of neonates with congenital brain malformations evaluated at a quaternary center with a neonatal neurocritical care service, neonates with disorders of neuronal migration/organization had the highest risk of neonatal-onset epilepsy compared with infants with other types of brain malformations. Neonates with disorders of early prosencephalic development and complex total brain malformations also had a clinically significant risk of epilepsy, whereas infants with hindbrain malformations had relatively lower risk. Similar to a prior study,¹³ our cohort of infants with congenital brain malformations and seizures also had a high mortality rate.

Our finding that disorders of neuronal migration and organization represent a high-risk group for early-onset epilepsy is in keeping with prior studies.^{6,18} In our cohort, polymicrogyria—a condition marked by excess and small gyri—was the single most common underlying malformation in children with neonatal-onset epilepsy. Polymicrogyria can have multiple genetic and acquired causes.^{19,20} Common neuropathological features in polymicrogyria include overmigration of cells, pial abnormalities, increased leptomeningeal vascularity, and altered lamination.^{6,20} The mechanisms of epileptogenesis may arise from several different pathways that lead to altered excitatory-to-inhibitory synaptic input ratios due to altered synaptic circuitry and enhanced excitatory activity, which may be due to synaptic short-circuitry in gyri fused across pial defects.⁶ Lissencephaly, which is a genetically diverse malformation characterized by absence or reduction in the number of sulci and gyri and a thickened cortex and is a malformation that commonly leads to intractable epilepsy,^{21,22} was the second most

TABLE 2.
Brain Malformation Categories, Subcategories, and Percent Monitored With cEEG in 132 Infants

Brain Malformation Categories/Subcategories	Total N = 132	Monitored With cEEG N = 74
Disorders of Early Prosencephalic Development	38 (29%)	23 (31%)
Corpus callosum dysplasia/hypoplasia	16/38 (42%)	8/23 (35%)
Complete corpus callosum agenesis	15/38 (39%)	11/23 (48%)
Septo-optic dysplasia	4/38 (11%)	2/23 (9%)
Holoprosencephaly	2/38 (5%)	2/23 (9%)
Anencephaly	1/38 (3%)	-
Disorders of Neuronal Migration/Organization	34 (26%)	23 (31%)
Polymicrogyria	15/34 (44%)	13/23 (57%)
Lissencephaly/pachygyria	6/34 (18%)	4/23 (17%)
Gyral simplification	5/34 (15%)	3/23 (13%)
Gray matter heterotopia	4/34 (12%)	2/23 (9%)
Frontal hypoplasia	3/34 (9%)	1/23 (4%)
Schizencephaly	1/34 (3%)	-
Disorders of Midbrain/Hindbrain Development	30 (23%)	10 (14%)
Cerebellar dysplasia/hypoplasia	8/30 (27%)	3/10 (30%)
Dandy-Walker malformation	6/30 (20%)	1/10 (10%)
Isolated cerebellar vermis hypoplasia	5/30 (17%)	-
Joubert syndrome	5/30 (17%)	4/10 (40%)
Pontocerebellar hypoplasia	3/30 (10%)	2/10 (20%)
Rhombencephalosynapsis	3/30 (10%)	-
Complex Total Brain Malformations	16 (12%)	11 (15%)
Complex total brain malformation NOS	8/16 (50%)	5/11 (45%)
Tuberous sclerosis complex	2/16 (13%)	1/11 (9%)
Aicardi syndrome	2/16 (13%)	2/11 (18%)
DiGeorge syndrome	1/16 (6%)	1/11 (9%)
L1CAM-associated malformation	1/16 (6%)	1/11 (9%)
Trisomy 18	1/16 (6%)	-
Walker-Warburg syndrome	1/16 (6%)	1/11 (9%)
Congenital hydrocephalus	14 (11%)	7 (9%)

Abbreviations:

cEEG = Continuous electroencephalogram

NOS = Not otherwise specified

Data are presented as n (%).

common malformation among children with epilepsy in our series. Although focal cortical dysplasia is a common cause of epilepsy (the most common brain malformation among children in a recent large series of children with severe infantile epilepsy),²³ it was not associated with neonatal-onset epilepsy in this series. This finding is likely due to the fact that focal cortical dysplasias can be difficult to detect, even on postnatal imaging,^{24,25} whereas most cases in our series were identified by prenatal MRI. Fetal MRI has technical limitations, which include low resolution and motion artifact that make visualization of thin fetal structures such as the marginal zone or cortical layers difficult to assess.^{26,27} Additionally, sensitivity can vary between malformations types, as heterotopia is less likely to be detected before 24 weeks gestation than polymicrogyria and schizencephaly.²⁸ For this reason, even malformations that can be detected on fetal MRI (e.g., congenital hydrocephalus, heterotopias, polymicrogyria, and lissencephaly) benefit from reimaging in the postnatal period to better delineate the anomaly, evaluate for associated pathologies, and monitor for changes in severity.^{29,30}

An important secondary finding is that the seizures were electrographic only in about one-quarter of infants with neonatal-onset epilepsy. This is in agreement with prior studies demonstrating that seizures in neonates are commonly subclinical,^{31–33} although children with acute provoked seizures are more likely to have any or exclusively subclinical seizures than children with neonatal-onset epilepsy.³ Altogether, these data reinforce the notion that relying on clinical evaluation alone is insufficient to detect seizures in high-risk infants and support ACNS recommendations for cEEG monitoring in high-risk neonates, including children with cerebral dysgenesis.⁸

Our results highlight the importance of cEEG monitoring during the neonatal period for children with congenital brain malformations; however, there may be other high-risk periods during which

monitoring could be useful for risk stratification and preventative interventions. In the EPISTOP study, there was a lower rate of infantile spasms or hypsarrhythmia among children with TSC who received frequent EEG and vigabatrin treatment at the onset of electrographic abnormalities.³⁴ Studies are needed to assess whether routine serial EEG monitoring in infancy for other high-risk brain malformations is of value. D'Gama and Poduri recently highlighted advances in precision treatment for epilepsy related to brain malformations, for example, mammalian target of rapamycin [mTOR] inhibitors for TSC and other conditions involving the mTOR pathway such as hemimegalencephaly and some focal cortical dysplasias.³⁵ The authors postulate that there will be significant advances in precision therapies for epilepsy related to malformations of cortical development in the coming decade.

Although we present a large cohort of neonates with congenital malformations and high-quality imaging and cEEG evaluated by neonatal experts, our work has limitations. First, although local guidelines recommend cEEG for all children with brain malformations, only half of the cohort was monitored with cEEG. Therefore, we may underestimate the risk of neonatal-onset epilepsy as seizures in neonates can be electrographic only or clinically subtle. In particular, neonates with midbrain/hindbrain malformations and congenital hydrocephalus were less likely to be monitored with EEG than children with disorders of neuronal migration/organization, disorders of prosencephalic development, or complex total brain malformations, which may have led to lower seizure detection rates in these children. For infants who were monitored, it is possible that rare subclinical seizures may have been missed outside the period of EEG monitoring, as EEG duration was variable and not standardized beyond a minimum of 24 hours. Second, diagnosis was by fetal or postnatal MRI. The technical limitations of

TABLE 3.
Clinical Characteristics of 18 Infants With a Congenital Brain Malformation and Neonatal-Onset Epilepsy

Case Number	Malformation Type	Malformation Subtype	Prenatal Diagnosis	Monitoring Indication	DOL 1st Seizure	Type of Seizures	EEG Background	ASMs	Genetic/Syndromic Diagnosis	Neonatal Death
1	Disorder of neuronal migration/organization	Polymicrogyria	No	Paroxysmal events	2	Electroclinical (autonomic)	Excess discontinuity, focal fast activity	None	DDX3X mutation	No
2	Disorder of neuronal migration/organization	Polymicrogyria	No	Paroxysmal events	1	Electrographic only Electroclinical (autonomic)	Attenuated left hemisphere, bursts of focal fast activity and abnormal sharps	Lorazepam (bolus) Levetiracetam (maintenance) Phenobarbital (bolus + maintenance)	-	No
3	Disorder of neuronal migration/organization	Polymicrogyria	No	Paroxysmal events	0	Electrographic only Electroclinical (clonic)	Frequent bicentral spikes	Lorazepam (bolus) Phenobarbital (bolus + maintenance)	Peroxisomal disorder	No
4	Disorder of neuronal migration/organization	Polymicrogyria	No	Encephalopathy	2	Electrographic only	Severely suppressed and discontinuous	Fosphenytoin (bolus) Phenobarbital (bolus + maintenance)	-	Yes
5	Disorder of neuronal migration/organization	Polymicrogyria	Yes	Paroxysmal events	20	Electroclinical (autonomic)	Asynchronous, excess discontinuity and bifrontal spikes	Phenobarbital (bolus + maintenance)	Congenital CMV	No
6	Disorder of neuronal migration/organization	Polymicrogyria	Yes	Paroxysmal events	1	Electrographic only	Occipital spikes	Phenobarbital (bolus + maintenance)	Zellweger spectrum disorder	Yes
7	Disorder of neuronal migration/organization	Lissencephaly/pachygyria	Yes	Abnormal imaging	1	Electrographic only Electroclinical (tonic)	Asynchronous, excess multifocal sharp waves and excess beta activity	Fosphenytoin (bolus + maintenance) Levetiracetam (bolus + maintenance)	TUBA1A mutation	No
8	Disorder of neuronal migration/organization	Lissencephaly/pachygyria	No	Paroxysmal events	18	Electroclinical (clonic)	Excess discontinuity, mild asynchrony and left > right hemisphere spikes	Levetiracetam (bolus + maintenance) Phenobarbital (bolus + maintenance)	Lissencephaly (DCX gene mutation)	No
9	Disorder of neuronal migration/organization	Lissencephaly/pachygyria	No	Paroxysmal events	1	Electrographic only	High amplitude and disorganized	Phenobarbital (bolus + maintenance) Phenytoin (bolus + maintenance)	Multiple anomalies (cleft lip/palate, midface hypoplasia, encephalocele)	Yes
10	Disorder of early prosencephalic development	Holoprosencephaly	Yes	Paroxysmal events	3	Electrographic only Electroclinical (tonic)	Asynchronous, continuous multifocal spikes and polyspikes	Carbamazepine (maintenance) Phenobarbital (bolus + maintenance)	-	Yes
12	Disorder of early prosencephalic development	Holoprosencephaly	Yes	Paroxysmal events	0	Electroclinical (myoclonic)	Report unavailable	Lorazepam (bolus)	-	Yes
11	Disorder of early prosencephalic development	Septo-optic dysplasia	No	Paroxysmal events	1	Electroclinical (clonic)	Normal	Lorazepam (bolus) Fosphenytoin (bolus + maintenance) Phenobarbital (bolus + maintenance)	-	No
13	Disorder of early prosencephalic development	Complete ACC	No	Paroxysmal events	2	Electrographic only	Excess discontinuity, asynchrony, excess multifocal sharps	Levetiracetam (maintenance) Phenobarbital (bolus + maintenance)	Coffin-Siris syndrome	No

14	Disorder of early prosencephalic development	Complete ACC	No	Abnormal imaging	0	Electrographic only Electroclinical (myoclonic)	Severe voltage attenuation	Fosphenytoin (bolus + maintenance) Levetiracetam (bolus) Lorazepam (bolus) Midazolam (infusion) Phenobarbital (bolus + maintenance) Levetiracetam (bolus + maintenance) Oxcarbazepine (maintenance) Topiramate (maintenance)	Suspected septo-optic dysplasia or trisomy 13	Yes
15	Disorder of early prosencephalic development	Corpus callosum dysplasia/hypoplasia	Yes	Encephalopathy	23	Electroclinical (clonic)	Excess discontinuity, asynchrony, multifocal sharps	Levetiracetam (bolus + maintenance) Oxcarbazepine (maintenance) Topiramate (maintenance)	Possible Mabry syndrome	Yes
16	Complex total brain malformation	Aicardi syndrome	Yes	Abnormal imaging	2	Electrographic only	Excess discontinuity, asynchrony, and depressed voltages	Lorazepam (bolus) Levetiracetam (maintenance) Oxcarbazepine (maintenance) Phenobarbital (maintenance) Topiramate (maintenance)	Aicardi syndrome	No
17	Complex total brain malformation	Aicardi syndrome	Yes	Abnormal imaging	2	Electrographic only Electroclinical (autonomic)	Excess discontinuity and asynchrony	Lorazepam (bolus) Levetiracetam (maintenance) Oxcarbazepine (maintenance) Phenobarbital (maintenance) Topiramate (maintenance)	Aicardi Syndrome	No
18	Disorder of midbrain/hindbrain development	Cerebellar dysplasia/hypoplasia	Yes	Paroxysmal events	60*	Electroclinical (autonomic)	Normal	Lorazepam (bolus) Phenobarbital (bolus)	CHARGE syndrome (CHD7 gene mutation)	No

Abbreviations:

ACC = Agenesis of the corpus callosum

ASMs = Antiseizure medications

CMV = Cytomegalovirus

DOL = Day of life (DOL0 is defined as the time of birth to the first 24 hours of life, DOL1 is 24–48 hours of life, etc)

EEG = Electroencephalography

PMA = Postmenstrual age

* Postmenstrual age 38 weeks.

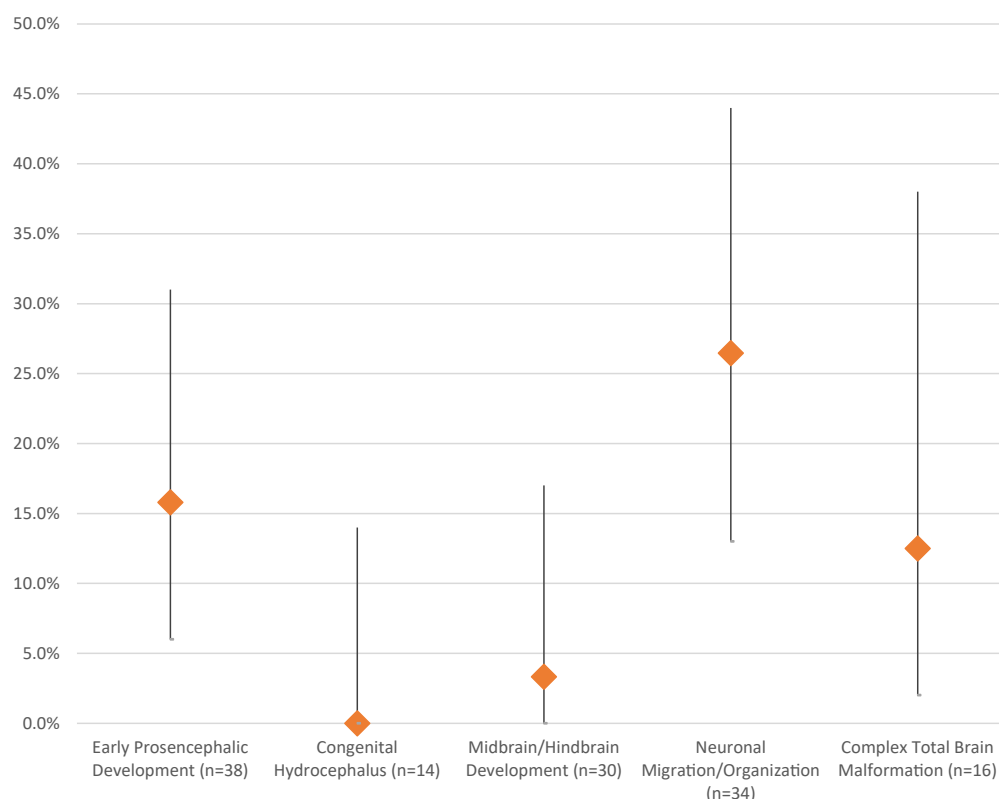


FIGURE. Risk of neonatal-onset epilepsy in 132 infants by the type of congenital brain malformation. Diamond shapes represent the observed risk of neonatal-onset epilepsy by the type of brain malformation. Vertical lines represent the 95% confidence interval. The color version of this figure is available in the online edition.

fetal MRI are discussed earlier. Nearly two-thirds of our cohort was identified prenatally, which suggests that, in spite of the limitations of fetal imaging, it can play an important role in identifying children at high risk for early-onset epilepsy. Since the advent of safe and widely available MRI, EEG is considered to have limited utility to distinguish between various malformations. Older studies report excess fast activity (alpha and beta) in children with disorders of neuronal migration and organization, a finding that was present in 44% of children with epilepsy in this category, and high-amplitude excess fast activity in children with lissencephaly, a finding that was present in one of three children in our study.^{36,37} Third, classification of brain malformations is challenging and terminology can differ depending on the reference used. Furthermore, classification schemes can evolve over time and make it apparent that multiple genetic defects can cause similar imaging findings (e.g., *LIS1*, *DCX*, and *ARX* in lissencephaly),³⁸ and single-gene pathway defects can lead to a variety of pathologies (e.g., mTOR signaling pathways causing focal cortical dysplasia type IIb, hemimegalencephaly, and ganglioglioma).¹⁸ Alternative classification schemes for disorders of neuronal migration/organization are based on the stages of cortical

development, beginning with neuronal and glial proliferation, progressing to neuronal migration and, ultimately, postmigrational development.⁷ We selected a classification scheme that focuses primarily on imaging patterns but used the results of genetic testing to classify syndromic malformations that carry a higher risk of epilepsy as “total brain malformations” as they are associated with widespread developmental abnormalities. Finally, selecting a cohort based on admission to the ICN and evaluation by a Neonatal Neurocritical Care Service may have led to a higher neonatal incidence of epilepsy than would be detected if children at lower acuity centers were included. Nonetheless, our cohort is representative children seen by quaternary care centers and therefore is widely applicable to most centers with Pediatric Epilepsy and Neonatal Neurology programs but limits our ability to generalize recommendations to children who receive a lower level of care in the newborn period.

Conclusions

Neonates with congenital brain malformations, and particularly disorders of neuronal migration/organization, are at a high risk for neonatal-onset epilepsy, which occurs in approximately 20–30% of individuals with these malformations. These findings help justify recommendations from the ACNS to monitor neonates with congenital brain malformations using cEEG in the neonatal period. Results from this study can also help inform prenatal counseling and postnatal management; however, detailed recommendations regarding postnatal evaluation for seizures are beyond the scope of this study. Future studies must address the timing, duration, and frequency of cEEG to optimize detection of early-onset epilepsy in children with congenital brain malformations.

TABLE 4.

Monitoring Indication for 74 Infants With Congenital Brain Malformations Who Received Continuous Video EEGs

Monitoring Indication	Monitored With cEEG N = 74	EEG Seizures N = 18
Abnormal imaging	32 (43%)	4 (22%)
Paroxysmal events	29 (39%)	12 (67%)
Encephalopathy	13 (18%)	2 (11%)

Abbreviations:

cEEG = Continuous electroencephalography

EEG = Electroencephalography

Data are presented as n (%).

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