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

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\textbf{Abstract}

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{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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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.\(^4\) 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.\(^5,6\) 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.\(^7\) 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 Volpe\(^8\) 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),\(^9\) (2) congenital hydrocephalus, which can be associated with additional major central nervous system abnormalities in up to 70% of cases,\(^10,11\) (3) disorders of midbrain/hindbrain development, which can also be associated with migratory disorders of the cerebral cortex,\(^12,13\) (4) disorders of neuronal migration/organization, with peak occurrence between the third and fifth months of gestation,\(^14\) (5) complex total brain malformations (defined as malformations spanning two or more categories).\(^15\) Malformations were further subcategorized by developmental anomalies within a category as follows:

1. Disorders of early prosencephalic development
   - Corpus callosum hypoplasia/dysplasia
   - Complete corpus callosum agenesis
   - Septo-optic dysplasia
   - Holoprosencephaly
   - Anencephaly

2. Congenital hydrocephalus
3. Disorders of midbrain/hindbrain development
   - Cerebellar dysplasia/hypoplasia
   - Dandy-Walker malformation
   - Isolated cerebellar vermis hypoplasia
   - Joubert syndrome
   - Pontocerebellar hypoplasia
   - Rhombencephalosynapsis

4. Disorders of neuronal migration/organization
   - Polymicrogyria
   - Lissencephaly/pachgyria
   - Gyral simplification
   - Gray matter heterotopia
   - Frontal hypoplasia
   - Schizencephaly

5. Complex total brain malformations
   - Complex total brain malformations not otherwise specified
   - Tuberous sclerosis complex (TSC)
   - Aicardi syndrome
   - DiGeorge syndrome
   - L1CAM
   - Trisomy 18
   - Walker Warburg syndrome

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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 seizures\(^5\)), 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.\(^16\) While all infants in this study technically met...
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 prosencephalochr 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, 17 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 prosencephalochr 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, 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. 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. Common neuropathological features in polymicrogyria include overmigration of cells, pial abnormalities, increased leptomeningeal vascularity, and altered lamination. 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. 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, was the second most
onset epilepsy.3 Altogether, these data reinforce the notion that 
or exclusively subclinical seizures than children with neonatal-
children with acute provoked seizures are more likely to have any 
NOS cEEG ¼ Abbreviations: 

Associated with neonatal-onset epilepsy in this series. This 
is likely due to the fact that focal cortical dysplasias can be dif 
possible that rare subclinical seizures may have been missed 
malformations, which may have led to lower seizure detec-
tion rates in these children. For infants who were monitored, it is 
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),24 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, sensi-
tivity 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, hetero-
Dandy-Walker malformation 
Isolated cerebellar vermis hypoplasia 
Joubert syndrome 
Pontocerebellar hypoplasia 
Rhombencephalosynapsis 
Complex Total Brain Malformations 
Complex total brain malformation NOS 
Tuberous sclerosis complex 
Aicardi syndrome 
DiGeorge syndrome 
L1CAM-associated malformation 
Trisomy 18 
Walker-Warburg syndrome 
Congenital hydrocephalus 

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),24 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 reimagining in the postnatal period to better delineate the anomaly, evaluate for associated pathologies, and monitor for changes in severity.25,10

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 subclinical31-33 although children with acute provoked seizures are more likely to have any or exclusively subclinical seizures than children with neonatal-onset epilepsy.1 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 prosenecphalic 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

| 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/pachygryria | 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%) |
| 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              | Attenuated left hemisphere, bursts of focal fast activity and abnormal sharp  | Lorazepam (bolus) |                | No             |
| 3           | Disorder of neuronal migration/organization     | Polymicrogyria       | No                 | Paroxysmal events     | 0               | Electrographic only              | Frequent bicentric spikes | Levetiracetam (maintenance) | Phenobarbital (bolus + maintenance) | No             |
| 4           | Disorder of neuronal migration/organization     | Polymicrogyria       | No                 | Encephalopathy        | 2               | Electrographic only              | Severely suppressed and discontinuous | Lorazepam (bolus) |                | Yes            |
| 5           | Disorder of neuronal migration/organization     | Polymicrogyria       | Yes                | Paroxysmal events     | 0               | Electrographic only              | Asynchronous, excess discontinuity and bifrontal spikes | Levetiracetam (bolus + maintenance) | Phenobarbital (bolus + maintenance) | Yes            |
| 6           | Disorder of neuronal migration/organization     | Lissencephaly/pachygyria | Yes               | Abnormal imaging      | 1               | Electrographic only              | Asynchronous, excess multifocal sharp waves and excess beta activity | Fosphenytoin (bolus) |                | No             |
| 7           | Disorder of neuronal migration/organization     | Lissencephaly/pachygyria | No                 | Paroxysmal events     | 18              | Electroclinical (tonic)          | Excess discontinuity, mild asynchrony and left > right hemisphere spikes | Levetiracetam (bolus + maintenance) | Phenobarbital (bolus + maintenance) | No             |
| 8           | Disorder of neuronal migration/organization     | Lissencephaly/pachygyria | No                 | Paroxysmal events     | 1               | Electrographic only              | High amplitude and disorganized | Levetiracetam (bolus + maintenance) | Phenobarbital (bolus + maintenance) | Yes            |
| 9           | Disorder of neuronal migration/organization     | Lissencephaly/pachygyria | No                 | Paroxysmal events     | 1               | Electrographic only              | Asynchronous, continuous multifocal spikes and polyspike | Fosphenytoin (bolus) |                | No             |
| 10          | Disorder of early prosencephalic development    | Holoprosencephaly    | Yes                | Paroxysmal events     | 3               | Electrographic only              | Asynchronous, continuous multifocal spikes and polyspike | Phenobarbital (bolus + maintenance) | Levetiracetam (bolus + maintenance) | Yes            |
| 11          | Disorder of early prosencephalic development    | Holoprosencephaly    | Yes                | Paroxysmal events     | 0               | Electroclinical (myoclonic)      | Report unavailable | Lorazepam (bolus) |                | No             |
| 12          | Disorder of early prosencephalic development    | Holoprosencephaly    | Yes                | Paroxysmal events     | 1               | Electroclinical (clonic)         | Normal | Lorazepam (bolus) |                | No             |
| 13          | Disorder of early prosencephalic development    | Complete ACC         | No                 | Paroxysmal events     | 2               | Electrographic only              | Excess discontinuity, asynchrony, excess multifocal sharp | Levetiracetam (maintenance) | Phenobarbital (bolus + maintenance) | No             |
14 Disorder of early prosencephalic development | Complete ACC | No | Abnormal imaging | 0 | Electroclinical only | Severe voltage attenuation | Fosphenytoin (bolus + 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) | Possible Mabry syndrome | Yes |

16 Complex total brain malformation | Aicardi syndrome | Yes | Abnormal imaging | 2 | Electrographic only | Excess discontinuity, asynchrony, multifocal sharps | Oxcarbazepine (maintenance) | Aicardi syndrome | No |

17 Complex total brain malformation | Aicardi syndrome | Yes | Abnormal imaging | 2 | Electrographic only | Excess discontinuity, asynchrony, and depressed voltages | Lorazepam (bolus) | Aicardi Syndrome | No |

18 Disorder of midbrain/hindbrain development | Cerebellar dysplasia/hypoplasia | Yes | Paroxysmal events | 60* | Electroclinical (autonomic) | Normal | Topiramate (maintenance) | 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.
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 | 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 (%)
References
1. Glass HC, Wu YW. Epidemiology of neonatal seizures. J Pediatr Neurol. 2009;7:13–17.
2. Glass HC, Shellhaas RA, Wusthoff CJ, et al. Controversy of seizures in neonates: a prospective cohort study. J Pediatr. 2016;174:98–103.e1.
3. Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: characteristics of a prospective US cohort. Neurology. 2017;89:893–895.
4. Olson HE, Yang E, Poduri A. Epileptogenic cerebral cortical malformations. In: Pellock JM, Nordli DR, Sankar R, Wheliss JW, eds. Pellock’s Pediatric Epilepsy: Diagnosis and Therapy. New York: Springer Publishing; 2016.
5. Grisar T, Lakaye B, de Nijs L, LoTurco J, Daga A, Delgado-Escueta AV. Myoclonus in epileptic encephalopathy. Brain. 2014;137:2787–2804.
6. Sarnat HB, Flores-Sarnat L. Excitatory/inhibitory synaptic ratios in polymicrogyria and Down syndrome help explain epileptogenesis in malformations. Pediatr Neurol. 2011;46:41–54.
7. Poretti A, Roltshaefer E, Huisman TA. Congenital brain abnormalities: an update on malformations of cortical development and infratentorial malformations. Semin Neurol. 2014;34:239–248.
8. Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society’s guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011;28:611–617.
9. Volpe JJ. Neurology of the Newborn. London: Elsevier Health Sciences; 2008.
10. Volpe P, Campobasso G, De Robertis V, Rembouskos G. Disorders of prosencephalic development. Prenat Diagn. 2009;29:340–354.
11. Varela MF, Miyabe MM, Oria M. Fetal brain damage in congenital hydrocephalus. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds. Jasper’s Basic Mechanisms of the Epilepsies. Bethesda, MD: Oxford University Press; 2012.
12. Etchegaray A, Juarez-Penalva S, Petracchi F, Igarzabal L. Prenatal genetic considerations in congenital ventriculomegaly and hydrocephalus. Childs Nerv Syst. 2020;36:1645–1660.
13. Menkes JH, Sarnat HB, Flores-Sarnat L. Child Neurology. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
14. Barkovich AJ, Millen KJ, Dobyns WB. A developmental and genetic classification for midbrain-hindbrain malformations. Brain. 2009;132:3199–3230.
15. Guerini R, Parrini E. Neuronal migration disorders. Neurobiol Dis. 2010;38:154–166.
16. Severino M, Geraldo AF, Utz N, et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain. 2020;143:2874–2894.
17. Tsuchida TN, Wusthoff CJ, Shellhaas RA, et al. American Clinical Neurophysiology Society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. J Clin Neurophysiol. 2013;30:161–173.
18. Barkovich AJ, Dobyns WB, Guerini R. Malformations of cortical development and epilepsy. Cold Spring Harb Perspect Med. 2015;5:a022392.
19. Epilepsy Phenome/Genome Project EXC. Diverse genetic causes of polymicrogyria with epilepsy. Epilepsia. 2021;62:973–983.
20. Squier W, Jansen A. Polymicrogyria: pathology, fetal origins and mechanisms. Acta Neuropathol Commun. 2014;2:80.
21. Rattana M, J MD. Lissencephaly. Treasure Island, FL: StatPearls; 2021.
22. Kolbjer S, Martin DA, Pettersson M, Dahlin M, Anderlid BM. Lissencephaly in an epilepsy cohort: molecular, radiological and clinical aspects. Eur J Paediatr Neurol. 2021;30:71–81.
23. Howell KB, Eggers S, Dalziel K, et al. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. Epilepsia. 2018;59:1177–1187.
24. Wong-Kisiel LC, Blawbomme T, Ho ML, et al. Challenges in managing epilepsy associated with focal cortical dysplasia in children. Epilepsy Res. 2018;145:1–17.
25. Wong-Kisiel LC, Tovar Quiroga DF, Kenney-Jung DL, et al. Morphometric analysis on TI-weighted MRI complements visual MRI review in focal cortical dysplasia. Epilepsy Res. 2018:140:184–191.
26. Kolak M, Herman-Sucharska I, Radon-Pokraka M, Stolarek M, Horbaczewska A, Huras H. The assessment of the usefulness of prenatal magnetic resonance imaging in the diagnosis of central nervous system defects. Diagnostics (Basel). 2021;11:1723.
27. Glenn OA, Barkovich AJ. Magnetic resonance imaging of the fetal brain and spine: an increasingly important tool in prenatal diagnosis, part 1. AJNR Am J Neuroradiol. 2006;27:1604–1611.
28. Glenn OA, Cuneo AA, Barkovich AJ, Hashemi Z, Bartha AI, Xu D. Malformations of cortical development: diagnostic accuracy of fetal MR imaging. Radiology. 2012;263:843–855.
29. Lerman-Sagie T, Leibovitz Z. Malformations of cortical development: from postnatal to fetal imaging. Can J Neurol Sci. 2016;43:611–618.
30. Nagaraj UD, Venkatesan C, Bierbrauer KS, Kline-Fath BM. Value of pre- and postnatal magnetic resonance imaging in the evaluation of congenital central nervous system anomalies. Pediatr Radiol. 2021. https://doi.org/10.1007/s00247-021-05137-1. Online ahead of print.
31. Wusthoff CJ, Dlugos DJ, Gutierrez-Colina A, et al. Electrographic seizures during therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. J Child Neurol. 2011;26:724–728.
32. Glass HC, Bonifacio SL, Peloquin S, et al. Neurocritical care for neonates. Neurocrit Care. 2010;12:421–429.
33. Scher MS, Alvin J, Gaus L, Minnigh B, Painter MJ. Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use. Pediatr Neurol. 2003;28:277–280.
34. Kotulska K, Kwiatkowski DJ, Curatolo P, et al. Prevention of epilepsy in infants with tuberous sclerosis complex in the EPISTOP trial. Ann Neurol. 2021;89:304–314.
35. Di Donato N, Timms AE, Aldinger KA, et al. Analysis of 17 genes detects microcephaly and epilepsy associated with focal cortical dysplasia in children. Epilepsy Res. 2021;143:1563.
36. Aicardi J. The place of neuronal migration abnormalities in child neurology. Can J Neurol Sci. 1994;21:185–193.
37. Gastaut H, Pinsard N, Raybaud C, Aicardi J, Zifkin B. Lissencephaly (agyria-pachygyria): clinical findings and serial EEG studies. Dev Med Child Neurol. 1987;29:167–180.
38. Di Donato N, Timms AE, Aldinger KA, et al. Analysis of 17 genes detects mutations in 81% of 811 patients with lissencephaly. Genet Med. 2018;20:1354–1364.