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

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Abstract

Background
While 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 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 pre- 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 18/132 (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% 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, 5/18 (28%) had only electrographic seizures, 13/18 (72%) required treatment with two or more anti-seizure medicines (ASMs), and 7/18 (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 ACNS recommendations for EEG monitoring during the neonatal period for infants with congenital brain malformations.
Introduction

While 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 (HIE) 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.\(^4\)

While 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/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 EEG monitoring.
The 2011 American Clinical Neurophysiology Society (ACNS) guidelines recommend continuous electroencephalogram (cEEG) monitoring for 24 hours in high risk neonates, including those with cerebral dysgenesis. 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 pre 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 compared to 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 a congenital brain malformations from 2008 to 2019. Infants were studied using a waiver of consent approved by the UCSF IRB. Inclusion criteria were congenital brain malformations identified on pre 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 (GA) <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\textsuperscript{9} 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),\textsuperscript{10} 2) congenital hydrocephalus, which can be associated with additional major CNS abnormalities in up to 70% of cases,\textsuperscript{11,12} 3) disorders of midbrain/hindbrain development, which can also be associated with migratory disorders of the cerebral cortex\textsuperscript{13,14}, 4) disorders of neuronal migration/organization, with peak occurrence between third and fifth months of gestation,\textsuperscript{15} 5) complex total brain malformations
(defined as malformations spanning two or more categories). 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 (ACC)
   c. Septo-optic dysplasia
   d. Holoprosencephaly
   e. Anencephaly

(2) Congenital hydrocephalus

(3) Disorders of mid/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
(5) Complex total brain malformations
   a. Complex total brain malformations not otherwise specified (NOS)
   b. Tuberous sclerosis complex (TSC)
   c. Aicardi syndrome
   d. Di George 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 (cEEG) monitoring for children with encephalopathy (defined as alterations in mental status, hypotonia, abnormalities in feeding or respiration, and seizures), 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 over 50% of 1-3 hours of recording time. 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 (RS), and seizures were classified according to the 2021 ILAE classification scheme of seizures in neonates\textsuperscript{10}. Neonatal onset epilepsy was defined, in keeping with the ILAE definition of epilepsy\textsuperscript{11}, as a disorder characterized by seizures (either electroclinical or electrographic only) identified prior to discharge from the intensive care nursery.

Analyses was performed using StataSE16 (College Station, TX) and Microsoft Excel (Redmond, WA). Binomial probability confidence intervals 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 5/132 (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 post-natal imaging in 117/132 (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 18/132 (14%) were diagnosed with neonatal onset epilepsy. Mortality was significantly higher for neonates diagnosed with epilepsy 7/18 (39%) compared with children who did not have seizures in the neonatal period 13/114 (11%, p=.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 compared with children with disorders of midbrain/hindbrain development and congenital hydrocephalus.

Neonatal onset epilepsy was diagnosed in 18/132 (14%, Table 3). The highest risk of epilepsy was among children 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%) (Figure 1). Children with polymicrogyria accounted for 6/18 (33%) and lissencephaly/pachygyria for 3/18 (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, 16/17 (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 13/18 (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 11/18 (61%) had seizures without clinical correlate at some point during the recording.

Thirteen of 18 (72%) infants were treated with two or more anti-seizure 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 to 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, while 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 over-migration 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,\textsuperscript{21,22} was the second most 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),\textsuperscript{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,\textsuperscript{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.\textsuperscript{26,27} Additionally sensitivity can vary between malformations types, as heterotopia is less likely to be detected before 24 weeks gestation compared to polymicrogyria and schizencephaly.\textsuperscript{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.\textsuperscript{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,\textsuperscript{31-33} although children with acute provoked seizures are more likely to have any or exclusively subclinical seizures as compared to children with neonatal onset epilepsy.\textsuperscript{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 tuberous sclerosis complex (TSC) who received frequent EEG and vigabatrin treatment at the onset of electrographic abnormalities.\(^3^4\) 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 tuberous sclerosis complex and other conditions involving the mTOR pathway such as hemimegalencephaly and some focal cortical dysplasias.\(^3^5\) 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 compared to 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 that 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 fetal MRI are discussed above. 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 classifications 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 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 manuscript. Future studies must address the timing, duration, and frequency of cEEG to optimize detection of early onset epilepsy in children with congenital brain malformations.
References

12. Etc
**Declaration of Interests:**

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.

Roxanne Simmons, MD, Ariadna Borras Martinez, MD, James Barkovich, MD, Maria Roberta Cilio, MD, Orit Glenn, MD, and Elizabeth Rogers, MD, have nothing to disclose.

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Table 1: Clinical characteristics, diagnostic evaluations, and outcome for 132 infants with congenital brain malformations evaluated for early onset epilepsy.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>N = 132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>64 (48%)</td>
</tr>
<tr>
<td>Premature (&lt;37 weeks GA)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Prenatal diagnosis</td>
<td>84 (64%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Evaluation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal MRI</td>
<td>49 (37%)</td>
</tr>
<tr>
<td>Neonatal MRI</td>
<td>117 (89%)</td>
</tr>
<tr>
<td>Neonatal EEG</td>
<td>74 (56%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal onset epilepsy</td>
<td>18 (14%)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>20 (15%)</td>
</tr>
</tbody>
</table>

Data are presented as n(%)

GA gestational age; EEG electroencephalogram; MRI magnetic resonance imaging
Table 2: Brain malformation categories, subcategories, and percent monitored with cEEG in 132 infants.

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

Data are presented as n(%)  
**cEEG** continuous video electroencephalogram; **NOS** not otherwise specified
### Table 3: Clinical characteristics of 18 infants with a congenital brain malformation and neonatal onset epilepsy.

<table>
<thead>
<tr>
<th>Malformation Type</th>
<th>Malformation Subtype</th>
<th>Prenatal Diagnosis</th>
<th>Monitoring Indication</th>
<th>DOL 1st Seizure</th>
<th>Type of Seizures</th>
<th>EEG Background</th>
<th>ASMs</th>
<th>Genetic/ Syndromic Diagnosis</th>
<th>Neonatal Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Disorder of neuronal migration/organization</td>
<td>Polymicrogyria</td>
<td>No</td>
<td>Paroxysmal events</td>
<td>2</td>
<td>Electroclinical</td>
<td>Excess discontinuity, focal fast activity</td>
<td>None</td>
<td>DDX3X mutation</td>
<td>No</td>
</tr>
<tr>
<td>2 Disorder of neuronal migration/organization</td>
<td>Polymicrogyria</td>
<td>No</td>
<td>Paroxysmal events</td>
<td>1</td>
<td>Electroclinical</td>
<td>Attenuated left hemisphere, bursts of focal fast activity and abnormal sharp waves</td>
<td>Lorazepam (bolus) Phenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>3 Disorder of neuronal migration/organization</td>
<td>Polymicrogyria</td>
<td>No</td>
<td>Paroxysmal events</td>
<td>0</td>
<td>Electrographic only</td>
<td>Electric (Conic)</td>
<td>Frequent bicentral spikes Lorazepam (bolus) Phenobarbital (bolus+maintenance)</td>
<td>Perosisoma l disorder</td>
<td>No</td>
</tr>
<tr>
<td>4 Disorder of neuronal migration/organization</td>
<td>Polymicrogyria</td>
<td>No</td>
<td>Encephalopathy</td>
<td>2</td>
<td>Electrographic only</td>
<td>Electric (Conic)</td>
<td>Severe suppression and discontinuous Fosphenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>5 Disorder of neuronal migration/organization</td>
<td>Polymicrogyria</td>
<td>Yes</td>
<td>Paroxysmal events</td>
<td>20</td>
<td>Electroclinical</td>
<td>Asynchronous, excess discontinuity and bifrontal spikes</td>
<td>Phenobarbital (bolus+maintenance)</td>
<td>Congenital CMV</td>
<td>No</td>
</tr>
<tr>
<td>6 Disorder of neuronal migration/organization</td>
<td>Polymicrogyria</td>
<td>Yes</td>
<td>Paroxysmal events</td>
<td>1</td>
<td>Electrographic only</td>
<td>Occipital spikes Phenobarbital (bolus+maintenance)</td>
<td>Zellweger spectrum disorder</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>7 Disorder of neuronal migration/organization</td>
<td>Lissencephaly/Pachygria</td>
<td>Yes</td>
<td>Abnormal imaging</td>
<td>1</td>
<td>Electrographic only</td>
<td>Asynchronous, excess multifocal sharp waves and excess beta activity</td>
<td>Lorazepam (bolus) Phenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>TUBASA mutation</td>
<td>No</td>
</tr>
<tr>
<td>8 Disorder of neuronal migration/organization</td>
<td>Lissencephaly/Pachygria</td>
<td>No</td>
<td>Paroxysmal events</td>
<td>18</td>
<td>Electroclinical (Conic)</td>
<td>Excess discontinuity, mild asynchrony and left-right hemisphere spikes</td>
<td>Lorazepam (bolus) Phenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>Lissencephaly (DCX gene mutation)</td>
<td>No</td>
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<tr>
<td>9 Disorder of neuronal migration/organization</td>
<td>Lissencephaly/Pachygria</td>
<td>No</td>
<td>Paroxysmal events</td>
<td>3</td>
<td>Electrographic only</td>
<td>High amplitude and disorganization</td>
<td>Lorazepam (bolus) Phenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>Multiple anomalies (cleft lip/palate, midface hypoplasia, encephaloc e)</td>
<td>Yes</td>
</tr>
<tr>
<td>10 Disorder of early prosencephalic development</td>
<td>Holoprosencephaly</td>
<td>Yes</td>
<td>Paroxysmal events</td>
<td>0</td>
<td>Electroclinical (Myoclonic)</td>
<td>Report unavailable</td>
<td>Lorazepam (bolus)</td>
<td>-</td>
<td>Yes</td>
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<tr>
<td>11 Disorder of early prosencephalic development</td>
<td>Holoprosencephaly</td>
<td>Yes</td>
<td>Paroxysmal events</td>
<td>1</td>
<td>Electroclinical (Conic)</td>
<td>Asynchronous, continuous multifocal spikes and polyspikes</td>
<td>Carbamazepine (bolus+maintenance)</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>12 Disorder of early prosencephalic development</td>
<td>Complete ACC</td>
<td>No</td>
<td>Paroxysmal events</td>
<td>1</td>
<td>Electroclinical (Conic)</td>
<td>Excess discontinuity, asynchrony, excess multifocal sharp waves</td>
<td>Lorazepam (bolus) Phenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>Coffer-Siris syndrome</td>
<td>No</td>
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<tr>
<td>13 Disorder of early prosencephalic development</td>
<td>Complete ACC</td>
<td>No</td>
<td>Abnormal imaging</td>
<td>0</td>
<td>Electrographic only</td>
<td>Severe voltage attenuation</td>
<td>Lorazepam (bolus) Phenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>Suspected septo optic dysplasia or trisomy 13</td>
<td>Yes</td>
</tr>
<tr>
<td>14 Disorder of early prosencephalic development</td>
<td>Complete ACC</td>
<td>No</td>
<td>Encephalopathy</td>
<td>23</td>
<td>Electroclinical</td>
<td>Excess discontinuity, asynchrony</td>
<td>Lorazepam (bolus) Phenytoin (bolus) Phenobarbital (bolus+maintenance)</td>
<td>Possible Mabry</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## *Postmenstrual age 38 weeks.*

**DOL** day of life (DOL0 is defined as time of birth to first 24 hours of life, DOL1 is 24-48 hours of life, etc); **PMA** postmenstrual age; **EEG** electroencephalography; **ASMs** anti-seizure medications; **ACC** agenesis of the corpus callosum; **CMV** cytomegalovirus.

**Table 4:** Monitoring indication for 74 infants with congenital brain malformations who received continuous video EEG.

<table>
<thead>
<tr>
<th>Monitoring Indication</th>
<th>Monitored with cEEG N=74</th>
<th>EEG Seizures N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal imaging</td>
<td>32 (43%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Paroxysmal events</td>
<td>29 (39%)</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>13 (18%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

Data are presented as n(%)
**Figure 1**: Risk of neonatal onset epilepsy in 132 infants by type of congenital brain malformation.

Diamond shapes represent the observed risk of neonatal onset epilepsy by type of brain malformation. Vertical lines represent the 95% confidence interval.