RPA Newborn Care Guidelines
Royal Prince Alfred Hospital
Seizures

Introduction

• Neonatal seizures are paroxysmal alterations in neurological function. This can be behavioural, motor or autonomic.¹
• Neonatal seizures can be clinical (with no EEG correlate), electroclinical (clinical associated with EEG findings) or electrographic (no clinical correlate).²
• A neonatal electrographic seizure is defined as a sudden, repetitive, evolving, and stereotyped event of abnormal electrographic pattern with amplitude of at least 2 µV and a minimum duration of 10 seconds.³
• Neonatal seizures are often a manifestation of neurological disease, they are rarely idiopathic and prognosis is dependent on the underlying cause.¹, ⁴⁻⁶ Where they are associated with poor neurodevelopmental outcome, it is not always known whether this is related to the seizure itself or the underlying cause.
• Most neonatal seizures will not persist into infancy and there is no evidence that treatment of clinical seizures with anticonvulsants improves outcomes. There are very few clinical trials looking at the efficacy of anticonvulsants for the treatment of neonatal seizures.⁷⁻⁹ These show there is partial suppression of clinical seizures with abnormal EEG activity persisting in a significant proportion of infants and insufficient data to determine if neonatal or long term outcomes are affected.⁷ However, there is consensus that neonatal clinical seizures should be treated, particularly if they are frequent, prolonged or have adverse effects on cardiorespiratory function.
• Treatment of electrical seizures detected by aEEG monitoring may reduce seizure burden.¹⁰⁻¹¹ RPA is collaborating in the Neonatal Electrographic Seizure Trial (NEST) to determine if neonatal or long term outcomes are affected by treatment of electrical seizures.

Incidence

RPA experience

In the 73 babies who developed clinical seizures over the period 1/1/2000 - 31/10/2004, the majority (38, 52%) were diagnosed with grade 2 or 3 hypoxic-ischaemic encephalopathy. The next largest category was intracranial haemorrhage and/or infarction (14, 19%). The remainder were either of unknown etiology (15, 20%), or uncommon conditions such as hyponatraemia (2, 3%), pyridoxine deficiency (2, 3%), hypoglycaemia (1, 1%) and neonatal abstinence syndrome (1, 1%). Many of these (30, 41%) were born at another hospital, but transferred to RPA because of the seizures. The incidence of seizures in inborn babies is thus 43 in approximately 17,500 births (0.25%).

Literature

• The incidence of seizures is higher in the neonatal period than in any other age group, with the majority occurring in the first week.¹, ¹²
• Clinical seizures occur in 0.5 to 3 / 1000 term live births.¹²⁻¹⁵ The incidence is higher in preterm birth 10 to 15 / 1000 live births.¹³⁻¹⁶
• Electrographic (clinically silent) seizure incidence is unknown. However, 80% to 90% of electrographic seizures do not have any associated clinical correlate.³ Electrographic seizures are thought to be more common in the preterm.¹³
Consequences

**Short term:** Prolonged seizures may cause cardiorespiratory impairment. They may be accompanied by hypoventilation and apnoea, causing hypoxia and hypercarbia with subsequent cardiovascular collapse. All of which, may predispose to secondary neuronal injury.

Long term: Prognosis depends on:

- **Aetiology of the seizure**:
  - Infants with global problems (perinatal asphyxia, cerebral dysgenesis, genetic syndromes) are at highest risk of cerebral palsy including spastic quadriplegia, global development delay and postneonatal epilepsy.  
  - Infants with focal lesions (intracranial haemorrhage, neonatal stroke) are at moderate risk of cerebral palsy and postneonatal epilepsy, but relatively low risk of spastic quadriplegia and global developmental delays. Survivors after intracranial haemorrhage have a relatively good prognosis.
  - Infants with idiopathic seizures also have a relatively good prognosis with <20% having a global developmental delay or postneonatal epilepsy.

- **Neurological exam:** abnormalities at initial assessment and persistent neurological abnormalities are associated with poor outcome.

- **Gestational age:** preterm infants with seizures are at higher risk.

- **Seizure characteristics:** increased likelihood of adverse / poor outcome associated with
  - Seizure type: subtle, generalised or 2 or more seizure types.
  - Status epilepticus prolonged or poorly controlled.
  - aEEG background: If there is persistent low voltage or burst suppression pattern this correlates with poor neurodevelopmental outcome in 65 to 90%.

Long term outcomes: Dependent on underlying aetiology, with higher incidence in preterm infants. The following are influenced by prognostic factors:

- **Mortality.**

- **Post neonatal seizures.** The incidence of epilepsy after neonatal seizures ranges 10-50%. The need for multiple antiepileptic drugs to control neonatal seizures, and the manifestation of predominantly nonfocal clonic seizures are the two strongest predictors of later epilepsy.

- **Adverse neurodevelopment outcomes including developmental delays, cerebral palsy and cognitive changes.**

Diagnosis

**Clinical:** Four main types of neonatal seizures are recognised clinically but the diagnosis may be inaccurate without EEG confirmation. The clinical assessment requires describing the abnormal movements suspected of being clinical seizures (see table).

1. Note types of movements, including limb and body involvement
2. Note duration and frequency of movements
3. Note whether movements occur during sleep or awake state
4. If the movements are arrested with limb restraint (suppressible), or
5. Provoked with tactile stimulation (inducible),

Movements that are *suppressible* and *inducible* are likely to represent normal jitteriness or tremors.

Benign neonatal sleep myoclonus:
• Occurs during REM / active sleep
• Not stimulus sensitive

Table 1: Clinical seizure types

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Incidence</th>
<th>Physical characteristics</th>
<th>EEG activity</th>
</tr>
</thead>
</table>
| Subtle       | Most common (50 – 75%) | Orofacial: Mouthing, chewing, lip smacking, blinking, eye deviation, fixed open stare  
Limb movements: eg Pedaling, boxing  
Autonomic: unstable blood pressure, tachycardia, central apnoea | Often no EEG correlate but EEG changes most likely to occur with eye signs |
| Clonic       | 23 – 40% | Repetitive jerking that cannot be suppressed if limb is held  
Focal or generalised  
DDx: jittering | Good correlation with EEG |
| Tonic        | 2 – 23%  | Stiffening, sustained posturing of the limbs or trunk or deviation of eyes  
Generalised or Focal (less common) | Focal : background often abnormal  
Generalised: often no EEG correlate |
| Myoclonic    | 8 – 18%  | Tend to occur in flexor muscle groups, rapid isolated jerks  
Focal, multifocal or generalised  
DDx: benign sleep myoclonus | Variable  
Focal: Often normal EEG |

Investigation:

aEEG with continuous 2-channel EEG: Allows early confirmation and treatment for a substantial proportion of infants with suspected clinical seizures. aEEG with 2 channel cEEG detects 55% of 12 channel conventional EEG detected seizures, and 73% of seizures >30 seconds and 87% >60 seconds.  

EEG: Clinical seizures are often difficult to diagnose and there is poor concordance between clinically evident seizures and electrical seizures present on EEG monitoring.  

Aetiology of neonatal seizures:  
1-3, 11, 13, 33, 35 In view of this, EEG should be arranged for all infants with clinical seizures.

The main causes are:
1. Hypoxic-ischaemic encephalopathy (HIE) ~50%
2. Intracranial haemorrhage (11%): subarachnoid (term > preterm), subdural (term infants with difficult deliveries) and peri/intraventricular (preterm infant)
3. Cerebral infarction (neonatal stroke) (10%): term infants
4. Congenital CNS structural abnormalities / cortical dysplasia (neuronal migration disorders causing cerebral cortical dysgenesis), (6%)
5. Intracranial infection (2%): meningitis > encephalitis

Less common causes are:
1. Inborn error of metabolism: amino and organic acidopathies, often seen after the infant starts feeding.
2. Electrolyte disturbances: hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyper- and hypo-natraemia,
3. Pyridoxine deficiency
4. Neonatal drug withdrawal
5. Trauma: delivery and non accidental injury
6. Benign familial neonatal seizures;  
   Autosomal dominant. Cases largely remit by 12 months and families can be given an excellent prognosis.
• Secondary to potassium channel KCNQ2 and KCNQ3 gene abnormalities: seizures begin around day 2 or 3.
• Secondary to sodium channel subunit gene SCN2A: seizures begin around 6 month but may be earlier.

7. Benign idiopathic neonatal seizures at day 5 of life which (‘fifth day fits’) 40
8. Unknown aetiology / idiopathic: 2 - 5% 37 – this is uncommon after a full diagnostic work up.
9. Progressive epileptic syndromes in the first year of life with onset in the neonatal period

Neuroimaging: use of imaging depends on the likely cause:

Cerebral US in combination with Doppler: 41 is an easily available modality that involves minimal or no disturbance to the neonate. However, cranial US has low sensitivity, especially in term babies with hypoxic-ischemic injury, reported to be normal in as many as 50% of neonates. It is also sometimes difficult to differentiate an ischemic stroke from a hemorrhagic infarction in the early stage because the echogenicity is similar. Cranial US is the primary imaging modality in neonates for detecting intraventricular hemorrhages (IVH), hydrocephalus and white matter changes.

AAP recommendations 42 for neuroimaging for term infants with encephalopathy include the following:

1. For infants with a history of neonatal encephalopathy AND significant birth trauma AND evidence for low haematocrit or coagulopathy:
   • Noncontrast CT should be performed to look for hemorrhage (level B).
   • If the CT findings cannot explain the clinical status of the neonate, MRI should be performed (level A).

2. For other neonates with acute encephalopathy: MRI [with DWI (diffusion weighted imaging) and MRS (Magnetic Resonance Spectroscopy)] should be performed between days 2 and 8 of life (level A). CT should be performed only if MRI is not available or if the neonate is too unstable for MRI (level A).

Management

1. Immediate:
   • Evaluation of ventilation and perfusion with resuscitation to commence immediately if required (See resuscitation guideline)
   • Hypoglycaemia should be looked for and treated promptly. Check the BGL immediately and if hypoglycaemic give 10% dextrose 2ml/kg IV bolus then follow with maintenance. (See hypoglycaemia guideline)
   • History: ask especially about maternal risk factors and complications of pregnancy, labour and delivery; risk factors for hypoglycaemia and sepsis; family history of metabolic / seizure disorders; previous unexplained perinatal death.
   • Physical examination: with particular attention to the neurological status.
   • Documentation: A detailed description of the seizure should be documented from the person(s) that witnessed the seizure.
2. If baby is on postnatal ward admit to the Newborn Care.
3. Investigations: All newborns with seizures should have the following investigations as a minimum to determine an underlying cause and treatment should be initiated quickly
   • Blood glucose level
   • Electrolytes: Na⁺, Ca²⁺, Mg²⁺
   • Full blood count
• Cranial ultrasound: to exclude gross CNS pathology, but is not effective at detecting subdural and epidural bleeds or identifying parenchymal injury.

Further investigations will be dependent on underlying aetiology.
• Acid – base status
• Blood culture
• Lumbar puncture: for CSF - microscopy and culture, glucose concentration (if low is suggestive of bacterial meningitis). PCR for herpes virus.
• Specimens for virology and congenital infections: TORCH (toxoplasmosis, rubella, CMV, herpes)
• Metabolic screen: urine for amino and organic acids
• Metabolic screen: blood for ammonia, lactate, pyruvate.
• Neurophysiology: formal 12 lead EEG, continuous EEG (BRAINZ monitor)
• Neuroimaging: CT, MRI

4. Underlying cause of seizure should be treated when known
• Hypoglycaemia (See hypoglycaemia guideline)
• HIE (See asphyxia guideline)
• IVH (See IVH guideline)
• Sepsis (See bacterial infection guideline, herpes guideline)
• NAS (See NAS guideline)
• Hypocalcaemia: Calcium gluconate 10% (0.22 mmol calcium/ml). Give 0.44 – 0.88 mmol/kg/day (2 - 4 ml of 10% solution/kg/day) as a continuous infusion IV. 22
• Hypomagnesaemia: MgSO₄ 50% solution (2 mmol/ml): Give 0.2 – 0.4 mmol/kg/dose every 12 hours IV or IM. 22
• Inborn error of metabolism is suspected: discontinue feeding as feeding may exacerbate the seizures and encephalopathy. Institute intravenous solutions. Contact paediatric metabolic disorders consultant.

5. Anticonvulsant medication:
• Indication for treatment of clinical seizures: 43
  o Prolonged > 3min
  o Recurrent > 3 in 1hour
  o Associated with cardiorespiratory compromise.

6. Treatment of electrical seizures:
• Treatment of electrical seizures detected by aEEG monitoring may reduce seizure burden. 10,11 It is unknown if treating electrical seizures improves other neonatal or long term outcomes.
• RPA is collaborating in the Neonatal Electrographic Seizure Trial (NEST) to determine if neonatal or long term outcomes are affected by treatment of electrical seizures.

Therapy (see Figure: Seizure treatment algorithm)

Systematic review 2 found two randomised controlled trials. Painter 1999 9 reported phenobarbital and phenytoin were similarly effective (RR 1.03 95% CI 0.96 to 1.62), controlling seizures in less than 50% of infants. Boylan 2004 8 randomised infants who failed to respond to phenobarbital to receive either lidocaine or midazolam as second-line agents. There was a trend for lignocaine to be more effective in reducing seizure burden (RR 0.40 95% CI 0.14 to 1.17) but both groups had similarly poor long term outcomes assessed at one year. There are safety concerns regarding lignocaine. 8
Phenobarbitone is used as a first-line more than 90% of the time in Europe, North America, and Australia. Phenytoin and a benzodiazepine are common second- or third-line anticonvulsant. Newer anticonvulsants have not been subjected to randomised controlled trials in newborns.

- Start with Phenobarbitone – loading dose 20mg/kg. Continued seizures 20 minutes after bolus complete – repeat loading dose 20mg/kg.
- If seizures are not controlled with maximum phenobarbitone, add Phenytoin – 20mg/kg loading dose over 30 minutes.
- In comparative studies of phenobarbitone and phenytoin both were found to be equally but incompletely effective either alone or in combination for the treatment of neonatal clinical seizures.
- Continue phenobarbitone 5 mg/kg daily for 3 days as per NEST study protocol.
- If a combination of phenobarbitone and phenytoin is ineffective, then commence midazolam initially as a bolus 200 micrograms/kg by slow IV bolus (3-5 minutes). If needed commence midazolam infusion at 1 microgram/kg/min and increase by 1 microgram/kg/min every 20 minutes until seizure control achieved to maximal 5 microgram/kg/min.

Additional agents:
- Lignocaines administered as a bolus of 4 mg/kg over 20 minutes followed by an infusion of 2mg/kg/hour. Monitor blood levels and discontinue by 48 hours.
- Clonazepam dose of 0.1 mg/kg every 24 hours (longer acting benzodiazepine that may be given orally).
- Consult paediatric neurologist.
- A trial of Pyridoxine should be performed in conjunction with EEG monitoring if pyridoxine deficiency is suspected in an infant with intractable seizures who does not have an underlying aetiology determined. Documenting cessation of seizures and normalisation of the EEG within minutes of IV pyridoxine often makes diagnosis. However, if there is no initial suppression on the EEG and seizures persist, then a second trial of pyridoxine should be given. Both trials of pyridoxine should be given with EEG monitoring.
Figure: Seizure treatment algorithm

Seizure event:
Assess infant clinically. If certain recurrent or prolonged clinical seizure commence treatment. Apply 2-channel continuous EEG / aEEG. If recurrent or prolonged clinical seizure clinical seizure confirmed then commence treatment. Consider enrolment in Neonatal Electrographic Seizure Trial (NEST)

Phenobarbitone 20 milligram/kilogram intravenous bolus, then 5 mg/kg daily for 3 days

Continued seizures 20 minutes after bolus complete

Phenobarbitone 20 milligram/kilogram intravenous (to total of 40 milligram/kilogram)

Continued seizures 20 minutes after 2nd bolus complete

Phenytoin 20 milligram/kilogram intravenous over 30 minutes

Continued seizures 20 minutes after dose of Phenytoin complete

Midazolam 200 micrograms/kilogram intravenous bolus over 3-5 minutes

Continued seizures after Midazolam bolus

Midazolam intravenous infusion commenced at 1 microgram/kilogram/minute and increased by increments of 1 microgram/kilogram/minute with each subsequent seizure episode to a maximum of 5 micrograms/kilogram/minute

If seizures persist, further treatment is at discretion of treating clinician
Table 2: Anticonvulsant Medications

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Indication for treatment</th>
<th>Loading dose</th>
<th>Maintenance</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>Seizures duration: ≥ 3 minutes OR Seizure frequency: ≥ 3 per hour</td>
<td>Phenobarbitone 20 milligram / kilogram intravenous bolus Repeat phenobarbitone 20 milligram / kilogram intravenous (to total of 40 milligram / kilogram)</td>
<td>5 mg/kg daily for 3 days Start 24 hours after the loading dose</td>
<td>Therapeutic level: 40 – 130 µmol/L Needs cardiorespiratory monitoring</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Inadequate response to phenobarbitone</td>
<td>20 mg/kg IV over 30 minutes</td>
<td>4 mg/kg/dose IV every 12 h Start 12 hours after the loading dose</td>
<td>Therapeutic level: 40-80 µmol/L Needs cardiorespiratory monitoring</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Inadequate response to phenobarbitone and phenytoin</td>
<td>200 micrograms/kg IV bolus over 3-5 minutes</td>
<td>Infusion commenced at 1 µg/kg/min and increased by increments of 1 µg/kg/min with each subsequent seizure episode to a maximum of 5 µg/kg/min</td>
<td>Needs cardiorespiratory monitoring</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Intractable seizures with no underlying aetiology determined</td>
<td>100 mg IV or IM stat (test dose)</td>
<td>50 – 100 mg daily oral</td>
<td>Pyridoxine trial(s) to be performed with EEG.</td>
</tr>
</tbody>
</table>

- There is limited neonatal experience in the use of other anticonvulsant medications including lamotrigine, carbamazepine, valproate, levetiracetam as second line agents for neonatal seizures. As such, the efficacy of these has not been adequately assessed in controlled studies.

Maintenance dosing should be restricted to infants at high risk of post neonatal epilepsy. The need for multiple antiepileptic drugs to control neonatal seizures, and the manifestation of predominantly nonfocal clonic seizures are the two strongest predictors of later epilepsy. Drug levels should be monitored to determine maintenance dosages because of the variable pharmacokinetics in this age group.

- **Paediatric neurology consultation:**
  Contact the Department of Neurology at either hospital and ask for the consultant on call, or if they are unavailable, contact the neurology fellow
  - Sydney Children’s Hospital (Randwick): Ph: 9382 1111
  - The Children’s Hospital at Westmead: Ph: 9845 0000

- **Discharge home and follow up:**
  - Prior to discharge, all babies to have a complete neurological examination documented in the clinical notes, discharge summary and the ‘blue book’.
  - All infants with neonatal seizures should receive follow-up by the attending consultant and the Developmental Follow - Up Clinic. If the infant is discharged home on anticonvulsants, then follow-up should be with the paediatric neurologist also.

**Key Points**
Key Points

| Clinical seizures are often difficult to diagnose and there is poor concordance between clinically evident seizures and electrical seizures present on EEG monitoring. EEG monitoring should be performed for diagnosis and treatment of seizures. | II 33, 35, 61 | B |
| aEEG with continuous 2-channel EEG allows early confirmation and treatment for a substantial proportion of infants with suspected clinical seizures. | II 10 | B |
| Phenobarbitone and phenytoin are equally but incompletely effective either alone or in combination. | II 7, 9 | B |
| Prognosis is most dependent on aetiology of seizures. | II 1, 13, 16-18 | B |

References

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