CLINICAL GUIDELINE	
Seizures: Neonatal	
Scope (Staff):	Nursing and Medical Staff
Scope (Area):	NICU KEMH, NICU PCH, NETS WA

This document should be read in conjunction with this DISCLAIMER

Neonatal seizures (NS) occur in 1.8-5 per 1000 live births, with majority occurring in the first few days of life (Nagarajan 2016, Jensen, 2009).

Seizures occur more frequently in the neonatal period than at any other time of life.

Key Points

- The time, duration and classification of seizures should be recorded. See appendix 1 for descriptions.
- Often in the same neonate more than one seizure type may be seen.
- Factors that provoke seizures (e.g. handling) and progression of events should also be noted.
- Neurological observations should be recorded on MR494 – Neonatal Neurological Observation Chart.

Aetiology

An underlying aetiology can be identified in nearly 90% of neonates with seizures with appropriate investigations.

Table 1: Aetiological classification of neonatal seizures

Hypoxic Ischaemic Encephalopathy
Hypoglycaemia, Hypocalcaemia, hypomagnesemia, hyponatremia, hypernatremia, hyperbilirubinemia
Intracranial haemorrhage: Subdural, Subarachnoid, IVH
Ischaemic infarction or Sino venous thrombosis
Intracranial infections: Meningitis; Encephalitis: HSV; Enterovirus
Congenital malformations of the CNS
Inborn errors of metabolism
Idiopathic
Intoxications: local anaesthesia

Loman et al., 2014

Differentiating epileptic seizures from seizure like activities: While dealing with a neonate with abnormal movement or behaviour, an important step is to know whether they are seizures or paroxysmal non epileptic motor phenomenon (Hart et al., 2015). The following

common abnormal movements need to be considered in the differential diagnosis of neonatal seizures (Table 2).

Table 2: Non-Epileptic movements which can mimic neonatal seizures

	Clinical features	**EEG**
Jitteriness/Tremor	Irregular, stimulus sensitive, disappear when the limb is held firmly	Normal
Benign neonatal sleep myoclonus	Repetitive, generalised, focal or multifocal rhythmic myoclonic jerks that occur during sleep in otherwise healthy normal neonates. Disappear when the neonate is awake	Normal
Motor automatisms	Repetitive stereotypical movements such as pedalling, cycling, boxing, swimming, drum beating type of movements or myoclonic jerks	Normal
Dystonic and tonic movements	Generalised stiffening of all four limbs	Abnormal usually but no seizures
Hyperekplexia	Excessive startle response	Normal
Paroxysmal extreme pain disorder	Flushing, stiffening or tonic phenomenon and bradycardia	Normal
Opsoclonus	Chaotic rapid multidirectional eye movements. Consider Neuroblastoma	Normal
Cardiac arrhythmias	Long QT syndrome, WPW syndrome etc	Hypoxic slowing during prolonged episodes

Diagnosis

Clinical examination alone has the potential to underdiagnose or over-report seizures (Murray et al., 2008, Nagarajan et al., 2012).

All infants with suspected seizures or at risk of seizures should be monitored with limited channel EEG with amplitude integrated aEEG (Brainz monitor). However, given the variable sensitivity and specificity, aEEG alone is not recommended for seizure detection in neonates (Rakshasbhuvankar 2017, Shellhaas et al., 2011).

It is important to request an urgent conventional multichannel video-EEG (V-EEG) as soon as possible.

Conventional Multichannel Electroencephalogram (V-EEG): The definitive diagnosis of neonatal seizures is based on their detection on V-EEG (Boylan et al., 2013). The American Clinical Neurophysiology Society's Guideline recommends that neonates at high risk for seizures be monitored with cV-EEG for 24 hours (Shellhaas et al., 2011).

- Difficulties in implementing this technology include the need for special training for the application and expertise for interpretation of the recording, variable access to equipment, and high cost. In the current clinical practice, a judicious combination of V-EEG and aEEG is often used for the diagnosis and management of neonates with seizures.

Investigations

Investigate and treat the underlying abnormality.

History

Table:3 Detailed history could provide clues to the cause of neonatal seizures.

Maternal diseases	Preeclampsia, Herpes Chorioamnionitis Antepartum haemorrhage, Excessive fetal movements
Maternal medications	Antidepressants Opioid analgesics Benzodiazepines Alcohol
History of perinatal asphyxia	Fetal heart rate monitoring Growth restriction Difficult labour Apgar scores Delivery room resuscitation details Type of delivery Cord blood gases
Parental description of the observed seizures	Ask if parents have taken a video of the episode. Encourage them to do so.

Clinical Examination

A thorough examination of the nervous system as well as other systems is important.

Initial investigation should focus on identifying conditions that are treatable and if untreated can lead to severe brain damage.

Table 4: Emergency investigations of potential treatable conditions

Delay in identification can be harmful

Condition	**Investigations**	
Metabolic	Blood glucose Plasma sodium Potassium Calcium Magnesium	Blood gas Lactate Ammonia Liver function tests Renal function tests
Infections	Full blood count CRP Blood culture CSF microscopy and culture	Throat and rectal swabs for HSV Blood PCR for HSV Urine microscopy and culture
Intracranial haemorrhage	Cranial ultrasound MRI or urgent CT scan if extradural or subdural haemorrhage is suspected	

Once the above investigations are completed, the next line of investigations will need to focus on conditions where curative therapy may not be available, but a definitive diagnosis will facilitate provision of supportive treatment and prognostication (Table 5).

Table 5: Investigations to make a diagnosis, in order to facilitate prognostication and supportive treatment (curative therapy may not available)

Condition	**Investigations**
Disorders of amino acid metabolism	Plasma, CSF and urine amino acids
Disorders of organic acid metabolism	Urine organic acids Plasma acyl carnitines
Mitochondrial and respiratory chain disorders	Blood and CSF lactate and pyruvate Muscle and/or liver enzymology Specific gene testing
Peroxisome disorders	Response to pyridoxine under EEG monitoring Urine, plasma and/or CSF aminoadipate semi aldehyde **or** Piperideine-6-carboxylate
Pyridoxal phosphate-responsive seizures (PNPO deficiency)	Response to pyridoxal phosphate, CSF amino acids and biogenic amines, urine vanillactate
Infections	CSF, blood, throat swab and rectal swab PCR for enterovirus, para-echo virus and other viruses.
Chromosome disorders, neonatal epileptic encephalopathies	Chromosome analysis Microarray Whole-exome sequencing Epilepsy gene panels
Idiopathic and refractory seizures	Liver biopsy Muscle biopsy Skin biopsy for DNA storage and analysis
Cerebral malformations, neuronal migration disorders, metabolic encephalopathies	MRI CT scan Cranial ultrasound

Imaging

The standard imaging studies are head ultrasound and MRI of the brain. If subdural or extradural haemorrhage is suspected, do an urgent CT scan.

Treatment

The main principles of management are anti-seizure medication, supportive management, and treatment of the underlying aetiology. Supportive management might necessitate the administration of IV fluids, mechanical ventilation and correction of hypotension, if required. Conditions such as meningitis, hypoglycaemia, hypocalcaemia, hypomagnesemia, electrolyte imbalances and HSV encephalitis should be treated aggressively.

Pharmacological treatment

Neonatal seizures still lack safe and effective treatment (Thoresen 2015). Treatment options are limited: what to treat, which antiepileptic drugs (AEDs) to use and for how long, are the issues that are still debated (Shetty, 2015).

Anticonvulsants

The commonly used anticonvulsants are Phenobarbitone (Booth 2004), Phenytoin (Booth 2004), Levetiracetam (Gowda 2019, Neolev trial), Midazolam (Sirsi 2008), Lignocaine Lundqvist, M., 2013), Clonazepam (Andre 1991), Topiramate (Filippi 2010) and Oxcarbazepine.

Refer to neonatal drug monograms for dose and administration, adverse effects and other details.

Request a neurology consult, especially if the seizures are not responding to first line therapy.

Phenobarbitone continues to be the first line anticonvulsant since the NeoLev study found 80% of neonates (24 of 30) randomized to PHB remained seizure free for 24 hours as compared with only 28% of subjects (15 of 53) randomized to Levetiracetam (p <0.001) (https://clinicaltrials.gov/ct2/show/results/NCT01720667).

Supportive and Follow-up Care

Treatment of seizures is only one aspect of care. Neuro-critical care for a neonate with seizures involves multiple disciplines including: neurology, neonatology, radiology, haematology, biochemistry, microbiology and many more. Neonates with seizures need to be followed up, assessed appropriately and early interventional strategies instigated proactively. Besides medical care, the family needs supportive care which should consider emotional, psychosocial and financial aspects, both in the short and long term.

Summary

The management of neonatal seizures is challenging. They are difficult to diagnose and treat and are associated with adverse outcomes.

The majority of neonatal seizures have no clinical correlates–they are electrographic only (subclinical) seizures.

The gold standard investigation to diagnose seizures is continuous V-EEG preferably for about 24 h; however, resource limitations are a hindrance to its universal applicability.

Initial investigations and management should focus on potentially treatable conditions, where delay in treatment can lead to worse outcomes.

MRI, ultrasound and CT scan can complement each other as imaging modalities.

Phenobarbitone, phenytoin, midazolam, levetiracetam and lignocaine are commonly used anticonvulsants in the neonatal period, but the evidence to support their efficacy and safety is limited. High quality RCTs evaluating various anticonvulsants in the neonatal population is needed (Nagarajan 2016).

Clinical Classification of Seizures

Type of Seizure	Clinical Features
Subtle (More common in the premature infant)	• Abnormal behaviour, autonomic or motor (not classified as other categories) • Ocular – eye deviation, staring episode, eyelid fluttering, repetitive blinking • Facial – repetitive sucking, mouthing, drooling, chewing, tongue protrusion • Limbs – cycling, boxing stepping movements • Autonomic – apnoea, tachycardia, hypertension, pupil changes, increased salivation
Clonic (Rhythmic jerks that do not stop with gentle restraint)	• Focal – 1 to 3 second jerking, localised to a body part • Multifocal or generalised – several body parts jerking simultaneously or migrating
Myoclonic	• Focal – flexor jerking of a limb • Multifocal or generalised – bilateral jerking of upper limbs +/- lower limbs
Tonic (posturing)	• Focal – posturing of a limb / trunk / neck • Multifocal or generalised – extension of lower limbs with either upper limb extension / flexion

Related CAHS internal policies, procedures and guidelines
Neonatology Guidelines • Brainz Monitor Low Impedance Needle Electrodes • Hypoxic Ischemic Encephalopathy (HIE) Neonatology Medication Protocols – • Clonazepam • Levetiracetam • Lidocaine • Midazolam • Phenobarbitone • Phenytoin

References and related external legislation, policies, and guidelines

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Appendix 1

Clinical Classification of Seizures

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