

NEONATAL SEIZURES

Introduction

Definition:

- Sudden, paroxysmal depolarisation of a group of neurones with transient alteration in neurological state. Possibly abnormal motor, sensory or autonomic activity with or without a change in conscious level.

Incidence:

- In babies born at term: 0.7-2.7 per 1000 live births, including preterm babies 0.15-3.5 per 1000 live births

Aetiology:

- Almost always due to underlying neurological pathology, idiopathic epilepsies rare; most commonly hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia (66%)

Pathophysiology:

- Excessive synchronous depolarization of neurons within the central nervous system

Clinical Presentation Classification

Subtle	Eyelid fluttering, eye deviation, fixed open stare, chewing, sucking, tongue thrusting, cycling, boxing, tachycardia, BP instability and apnoea.
Clonic	Rhythmic jerking, consciousness usually preserved. Focal, multifocal or generalised. Often correlate with a structural lesion.
Myoclonic	Rapid, isolated jerks. Rare in neonatal period and usually indicates diffuse cerebral disease. Focal, multifocal or generalised.
Tonic	Extension of upper and lower limbs accompanied by pronation of arms and clenching fists. Often less than a minute and seen most commonly in the first 24 hrs of life following an hypoxic-ischaemic event

- Typically focal start, evolving in amplitude, duration and waveform morphology.
- Not all clinical seizures are accompanied by electroencephalographic seizure discharges (seizure discharges in deep cerebral structures not transmitted to surface EEG electrodes).
- Distinction from non-seizure paroxysmal movements can be difficult – differential diagnoses include jitteriness, benign sleep myoclonus and other motor phenomena.
- Normal motor activity: often stimulus – sensitive, can be suppressed by restraint, gaze and eye movements normal, no autonomic changes.

Principles of Management

1. Resuscitation and supportive measures:

- Follow standard Neonatal Life Support guidance.
- Check blood sugar and correct hypoglycaemia urgently.

- Ensure appropriate cardiovascular monitoring: saturations, ECG and blood pressure.
- Consider cerebral function monitoring but do not delay treatment.

2. Assessment and treatment of the underlying cause:

History:

- See table 1 for possible causes of neonatal seizures.

Neurological examination:

- Examination of the pupils, level of consciousness, muscular tone, muscular reflexes, newborn reflexes (suck, grasp reflexes), gag reflex, signs of significant birth injury (subgaleal haematoma, skull fracture).

Mandatory and urgent tests:

- **Glucose** (BM and lab)
- Blood gas
- Urea and electrolytes, calcium, magnesium
- Blood culture
- aEEG or EEG (Seizure activity is not necessarily accompanied by clinical signs (subclinical), especially following anti-epileptic drugs (AED))
- Consider cranial ultrasound and lumbar puncture

Further Investigations (modify according to history):

- Blood: clotting, liver function tests, amino acids, ammonia, congenital infection screen, Troponin T if HIE possible, consider CGH array and chromosomes
- Urine: toxicology, amino acids and organic acids, reducing sugars
- CSF: MC&S, protein, glucose, consider lactate, glycine and herpes PCR
- Others: MRI, EEG
- Further investigations (including specific genetic tests) in discussion with specialist team.

Table 1: Cause, presentation and treatment of underlying causes of neonatal seizures:

Diagnosis	Presentation	Treatment
Hypoxic-ischaemic injury	Term baby, history of extensive resuscitation. Seizures usually within 24 hrs	See guidelines for HIE
Intracranial causes	Preterm infant: fits within 24-72 hrs following IVH Term infant: HIE as above, antenatal cerebral infarction / bleed, structural malformations of brain	Consider urgent cerebral imaging and referral to neurosurgical team
Infection	Consider bacterial/viral meningitis, herpes encephalitis, CMV, toxoplasmosis	Treat for sepsis (see protocol), consider acyclovir
Hypoglycaemia	Likely IUGR or infant of diabetic mother. Galactosaemia, glycogen storage disease. Hypoglycaemia may be result rather than cause of seizures.	10% dextrose, 2.5 ml/kg IV bolus, repeat after 10 minutes if BM < 2.6 mmol/l (see hypoglycaemia protocol)
Hypocalcaemia (correct for albumin)	Sick infant, IUGR, infant of diabetic mother, high phosphate intake, maternal	10% calcium gluconate, 1-2 ml/kg IV over 5-10

	diet low in Vitamin D, exchange transfusion.	minutes with ECG monitoring
Hypomagnesaemia	Rare but may co-exist with hypocalcaemia	50% magnesium sulphate 0.2 ml/kg IV
Hyponatraemia	High maternal oral water intake during labour, infants with reduced urine output (e.g. RDS, HIE) or preterm infants with high renal losses +/- diuretics. Seizures unlikely if serum sodium > 125 mmol/l	2-3 ml/kg 3% NaCl bolus, then slow intravenous correction over 24 hours, only fluid restrict when hyperhydration proven
Hypernatraemia	Usually result of dehydration, rarely inappropriate intake	20 ml/kg 0.9 % NaCl bolus, rehydrate, decrease sodium intake
Inborn errors of metabolism	Consanguineous parents, metabolic acidosis, seizures difficult to control, worse with introduction of feeds. Consider maple syrup urine disease, urea cycle deficits, non-ketotic hyperglycinaemia	Whilst investigating stop milk feeds, ensure adequate calorie intake as IV dextrose, correct acidosis Discuss with specialist team
Pyridoxine deficiency	Seizures unresponsive to anticonvulsant therapy, may have a family history	Trial of pyridoxine under EEG monitoring. (see recommendations below) Discuss with specialist team
Drug withdrawal	Maternal history	See withdrawal protocol
Drug toxicity	Theophylline , local anaesthetics	Depending on specific drug
Idiopathic	Benign familial epilepsy	None required

Pharmacological treatment of neonatal seizures (please refer to Neonatal Formulary for dosing)

- Medically treat seizures **occurring 3 or more times/hour or lasting > 2 minutes.**
- See flow diagram (figure 1) below for choice of drug and dosing recommendations.
- Phenobarbital, benzodiazepines and phenytoin still the most commonly used medications to treat neonatal seizures.
- Ensure that each medication is sufficiently loaded and continued when loading with a second drug.
- Myoclonic events have been described after administration of anticonvulsants (e.g. midazolam).
- Seek specialist advice in cases with therapy refractory seizures.

Phenobarbital:

- Drug of first choice. Broad experience, good safety profile but evidence of possible neuronal apoptosis and long term effects with impairment of neuro-developmental outcome.
- Aim for a maximum level of 40 mg/L (range 15-40 mg/L), avoid levels > 50 mg/L.

- Seizure response rates after one loading dose 33% to 40%, after a total dose of 40 mg/kg up to 77%.
- Long half-life in neonates (140 hrs in asphyxiated neonates).
- Potentially improving outcome when given early in HIE.
- Reported to have potential positive effect in combination with Phenytoin.

Levetiracetam (Keppra®):

- Seemingly effective and well tolerated but lacking evidence from randomised controlled trials regarding dosage, efficacy and safety (RCT currently ongoing). Increasingly used as second line in neonatal patients.
- No level monitoring recommended
- Renal elimination, dose reduction only recommended for severe renal impairment (increased creatinine x 3 and UO < 0.7ml/kg/hr in 24 hrs or anuria over 12 hrs).
- Reported 86% success rate in 1hr.

Benzodiazepines:

- Commonly used as second or third line therapy. Preferred use of Midazolam (rapid onset of action, advantage of dose titration according to response) but can also use lorazepam, diazepam or clonazepam. Potentially rectal diazepam or buccal midazolam if no venous access available.
- Close monitoring for cardiorespiratory depressive effects.

Pyridoxine / Pyridoxal-5-phosphate (PLP) / Folinic acid / Biotin:

- Rare metabolic disorders can present as neonatal seizures. Consider trial in case of seizures refractory to standard anticonvulsants especially with unknown cause. Pyridoxine-deficient epilepsy is rare but treatable!
- EEG- and cardiorespiratory monitoring for potential significant apnoeas.
- Start with pyridoxine but consider trial of PLP and/or folinic acid and/or biotin if unresponsive to pyridoxine (see literature recommendations below, seek specialist advice).

Phenytoin:

- Still one of the most commonly used drugs for neonatal seizures but controversial due to side effects
- High risk of venous irritation/soft tissue necrosis – establish secure venous access! Do not dissolve in dextrose; flush intravenous line with normal saline before and after use of phenytoin.
- Close cardiovascular monitoring as may cause severe refractory bradycardia, arrhythmia (even asystole) and significant hypotension - ADMINISTER VERY SLOWLY, do not exceed 1 mg/kg/min.
- DO NOT USE in **cooled babies** (contraindicated in sinus bradycardia) or in **combination with lidocaine** (potential additive cardiodepressive effects).
- Aim for a plasma level of 6-15mg/L (25-60 micromol/L).
- Equally effective as phenobarbital but more potential side-effects, unpredictability of metabolism in neonates, need for frequent blood level monitoring.
- Reported to have potential positive effect in combination with Phenobarbital.

Lidocaine:

- Can be used for refractory seizures as third line treatment. Narrow therapeutic window, potential to cause cardiac arrhythmias or hypotension, can induce seizures at high doses.
- DO NOT USE **in combination with phenytoin** as may have additive cardio-depressive effects.

- DISCONTINUE IMMEDIATELY IN CASE OF ARRHYTHMIA, avoid in neonates with congenital heart disease.
- Adjust dose during therapeutic hypothermia as higher risk of cardiotoxicity
- Suspected threshold for cardio-neurotoxic adverse effects in neonates: >9mg/L.

Paraldehyde:

- Can be used as initial treatment if no intravenous access available.
- Rectal administration.

Alternative antiepileptic drugs:

- Various alternative drugs available (e.g. valproate, bumetanide, lamotrigine, topiramate, vigabatrin or felbamate etc.).
- No neonatal evidence available. Not recommended without specialist advice.

Maintenance therapy:

- If further convulsions unlikely stop anticonvulsive treatment.
- If further convulsions likely continue maintenance treatment and withdraw gradually with an aim to remain on monotherapy.
- If maintenance therapy continued, consider referring to paediatric epilepsy department.
- Commence maintenance treatment 12 hours after initial therapy.
- If neurological examination and inter-ictal EEG normalise in asphyxiated infant further seizures unlikely.
- Longer-term therapy may be required in infants with structural brain pathology, abnormal neurology and/or abnormal EEG
- Consider potential long term neurodevelopmental side effects, especially with phenobarbital.

Prognosis:

- Seizures in early life may result in permanent anatomical and functional alteration and enhance epileptogenicity.
- Long term outcome is determined by underlying aetiology, seizure type, duration and EEG findings.
- Generally good outcome for short lived, easily controlled seizures, sustained refractory seizures reflect a more severe brain disorder.
- Focal clonic and tonic seizures are associated with a relatively good outcome while generalised tonic posturing and motor automatisms are associated with poor outcome.
- Excellent prognosis for hypocalcaemia and benign familial neonatal seizures.
- High incidence of long term complications and mortality rate in HIE, symptomatic hypoglycaemia, intracranial haemorrhage and meningitis.

Medical Treatment for Neonatal Seizures

