East Midlands Neonatal
Operational Delivery Network

NETWORK GUIDELINE

Guideline:	**Management of Seizures in a Newborn (North Hub)**
Version:	**1**
Date:	**October 2020**
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Approval:	**EMNODN Clinical Governance Group**
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Consultation:	**EMNODN Clinical Governance Group**
Distribution:	**Neonatal Units within EMNODN North Hub**
Risk Managed:	**How to manage seizures appropriately**

This document is a guideline. Its interpretation and application remains the responsibility of the individual clinician, particularly in view of its applicability across the different Trusts in the East Midlands Neonatal Operational Delivery Network - North Hub. Please also consult any local policy/guideline document where appropriate and if in doubt contact a senior colleague.

Caution is advised when using guidelines after a review date.

REVIEW AND AMENDMENT LOG

Version	Type of Change	Date	Description of Change
1	New guideline	May 20	-

Abbreviations used in this guideline:

BE:	Base excess
CFM:	Cerebral function monitoring
CRP:	C-reactive protein
CT:	Computed tomography
EEG:	Electroencephalogram
aEEG:	Amplitude-integrated electroencephalography
cEEG:	Continuous electroencephalography
HIE:	Hypoxic-ischaemic encephalopathy
HSV:	Herpes simplex virus
IEM:	Inborn error of metabolism
MRI:	Magnetic resonance imaging
PCR:	Polymerase chain reaction
Sa02:	Oxygen saturations
TORCH:	Toxoplasmosis, rubella, cytomegalovirus, herpes simplex, HIV

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Appendices:

1. Introduction

Seizures are the most common and distinctive manifestation of neurological disturbance in the neonatal period and have the highest incidence within the first four weeks of life[1]. They pose a major risk for death or subsequent neurological disability and can independently cause adverse neurodevelopmental outcomes in high-risk neonates[2]. There are also possible harmful effects of anticonvulsants on the developing brain.

The estimated incidence is 1.5-5.5 per 1000 births in term newborns and 10-100/1000 in preterm infants[3,4]. Most seizures are acute symptomatic (85%), but a small number of epileptic syndromes exist (15%)[5]. There is no universally accepted evidence based guidance concerning neonatal seizures.

2. Aetiology

A seizure is a stereotypic, paroxysmal spell of altered neurological function, due to abnormal electrical activity in the brain. Neonatal seizures are significant because they are rarely idiopathic (Table 1 for possible aetiologies, Table 2 for risk factors). Prompt diagnosis of any underlying condition is important; some specific treatments and when applied early, may improve outcome.

Table 1: Aetiology of Neonatal Seizures

- **Hypoxic-ischaemia** (Prenatal, Perinatal, Postnatal)
- **Cerebrovascular disorders** (Perinatal arterial ischaemic stroke, intraventricular haemorrhage, haemorrhagic parenchymal infarction, subarachnoid/subdural haemorrhage, Cerebral venous sinus thrombosis)
- **Intracranial infections** (Encephalitis, meningitis, abscess)
- **Transient metabolic / electrolyte disturbances** (hypoglycaemia, hypocalcaemia/ hypomagnesaemia, hypernatraemia/ hyponatraemia)
- **Maternal drug withdrawal** (Sedatives, alcohol, opiates, barbiturates)
- **Inborn errors of metabolism** (IEM) (Appendix 4)
- **Malformations of cortical development**
- **Neurocutaneous syndromes** (tuberous sclerosis, incontinentia pigmenti, Sturge-Weber syndrome)
- **Neonatal epileptic syndromes** / Epileptic encephalopathies (Ohtahara syndrome, early myoclonic encephalopathy)
- **Idiopathic benign neonatal seizures** (Familial, non-familial)

In term infants, the most **common causes of seizures are HIE, ischaemic stroke and intracranial haemorrhage[6].** In extremely preterm infants, the most common cause is intracranial haemorrhage; the presence of seizures is associated with adverse outcomes[7,8]. The timing of seizure onset may help to determine the possible aetiology[9].

IEM are a rare cause of seizures but important to **consider in treatment resistant seizures.** The main mechanism of seizure generation is by accumulation of toxic metabolites, impaired neuronal function , associated brain malformation and vitamin or cofactor dependency[10] (See Appendix 4: Inborn errors of metabolism mainfestion with seizures).

Table 2: Risk factors for neonatal seizures
1. Maternal • Advancing maternal age >40 years • Nulliparity • Pre-existing/gestational diabetes mellitus 2. Intrapartum • Evidence of fetal distress • Placental abruption, cord prolapse, prolonged second stage • Maternal pyrexia, chorioamnionitis 3. Infant • Lower gestational age in preterm infants • Low birth weight • Post term > 42 weeks • Male sex

3. Clinical Manifestations

Four main types of seizures are recognised, and within each type seizures can be **unifocal, multifocal or generalised**. In the newborn, there is the unusual problem of electro-clinical dissociation[11]. Only around one third of term infants with electrical seizures have overt clinical signs. 70% of abnormal movements have no correlating EEG seizure activity[12]. See Table 3 below and Appendix 1 for EEG correlation and clinical association.

Neonatal EEG (electrical or electrical-clinical) seizures have a sudden change in the EEG, repetitive waveforms evolving in morphology and frequency and a duration of at least 10 seconds.

Table 3: Types of seizures and their clinical manifestations[11]

Type of seizure	Clinical manifestations	Correlation with 12 lead EEG findings
Subtle (more common in term babies)	Eye signs – eyelid fluttering, eye deviation, fixed open stare, blinking Apnoea (not associated with bradycardia in seizures) Body movements- cycling/peddling, limb posturing Oral signs- mouthing, chewing, lip smacking Autonomic- vasomotor (tachycardia, unstable BP), pallor, apnoea, increased salivation/secretions	Often no EEG changes – most likely with ocular manifestations
Clonic	Repetitive rhythmic jerking, distinct from jittering.	Usually EEG changes present

(focal or multifocal)	Rapid twitch followed by slow relaxation.	
Tonic (more common in preterm babies)	Stiffening, decerebrate rigidity or decorticate posturing. Focal tonic head or eye turning. Sustained contraction (flexion/extension).	EEG variable
Myoclonic (Rare - generalised or focal)	Rare. Resemble clonic movements but are quicker and appear more "jerky" with a predilection for flexor muscles. ***Note: sleep myoclonus is benign and therefore normal***	EEG often normal, although background EEG can be abnormal

4. Diagnosis

Neonatal seizures are a common neonatal emergency. Confirmation of seizures should initiate urgent and appropriate **clinical and laboratory evaluation** for aetiological cause. A full history and examination should be performed, together with urgent comprehensive biochemical tests for correctable metabolic disturbances (first line investigations).

4.1 History

Antenatal history:

- Routine anomaly scan findings
- Illness during pregnancy
- Maternal morbidities e.g. diabetes
- Frequency & character of movements in utero (classically, seizures in utero can mimic hiccoughs)
- Maternal drug use – prescribed or illicit
- History of infections (including genital herpes)

Perinatal and birth history:

- Prolonged rupture of membranes & risk factors for infection
- Eclampsia
- Labour and delivery complications (trauma, fetal distress)
- Evidence of intrapartum hypoxia:
  (pH <7.00; BE -16 or worse in cord or early (<1hr old) capillary or arterial gas or Apgar $\leq$ 5 at 10 mins, need for continued resuscitation at 10 mins of age)

Family history of seizures:

History of **similar presentation and transient nature in siblings or parents** would suggest Benign Familial Neonatal Convulsions. Some neuro-cutaneous disorders may be inherited. A family history of metabolic disorder should be considered especially if consanguineous marriage.

4.2 Age at onset

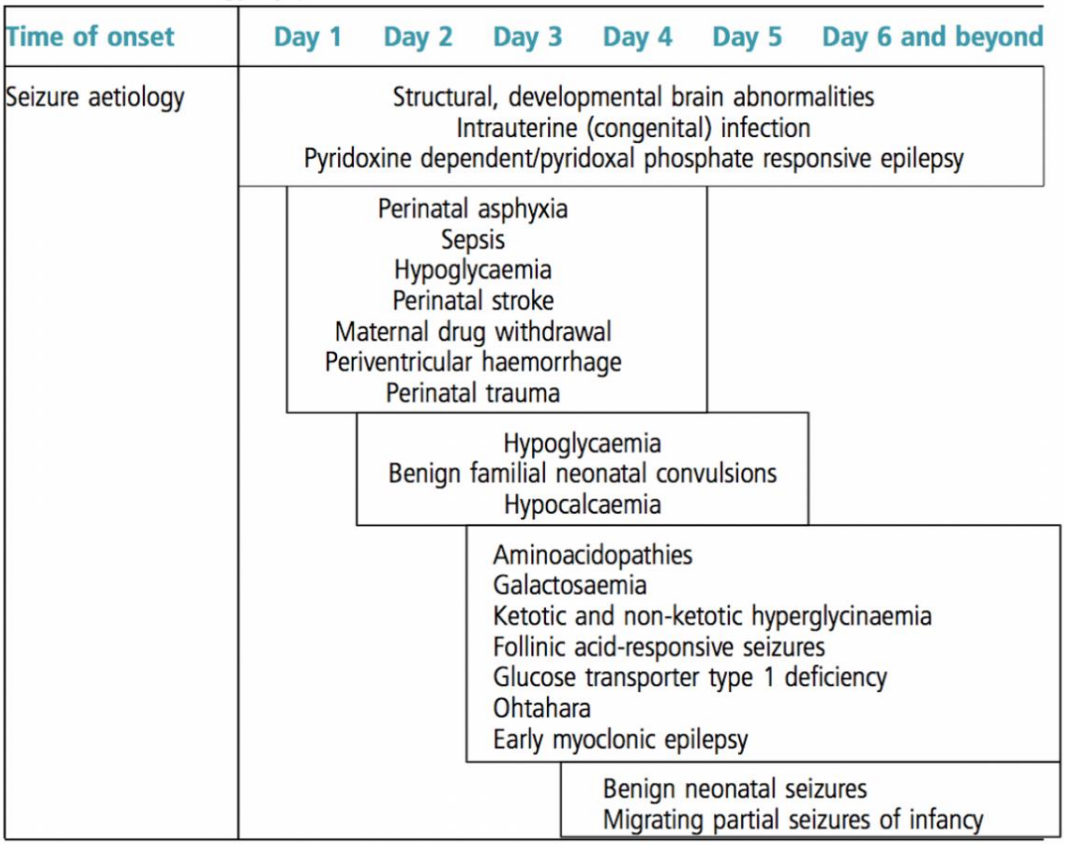


Figure 1: Aetiology of seizures by predominant time of onset[13,14]

4.3 Description of seizure

- Type of seizure (as above)
- Frequency and duration
- Clear onset and offset
- Any provoking factors
- Relationship to sleep pattern
- Association with eye deviation or autonomic disturbance
- Document whether they are stopped or modified with posture or gentle restraint (unlikely seizure).

4.4 Examination

See **Appendix 2** for key findings in general physical examination for the newborn with suspected seizures.

Physical examination– complete systematic examination including the following:

- Head circumference
- Skin/cutaneous examination
- Ophthalmological examination (often 2nd line)
- Facial (or other) dysmorphism or congenital anomalies
- Neurological examination

5. Investigations

Investigations can be considered as **1st line –** to follow history and examination in the event of confirmed or highly suspected seizures (Table 4 below), **and 2nd line** – initiated in tertiary NICU after referral and discussion with on-call Neonatologist and/or paediatric neurologists.

Table 4: Investigations of seizures[15]

Evaluation	First line investigations	Second-line investigations
Clinical	Complete history, general and neurological examination	Dilated ophthalmologic exam Pyridoxine/pyridoxal phosphate therapeutic trial
Blood	Sodium (UE), glucose, ionised calcium, magnesium, phosphate, LFT, blood gas (pH, bicarbonate, lactate), bilirubin FBC, coagulation screen CRP, blood culture, HSV PCR	Carnitine, acylcarnitine, TFT, carbohydrate deficient transferrin, biotinidase enzyme activity, ammonia, lactate, Urate, pyruvate, amino acids, TORCH titres
Urine	Urine culture Toxicology screen if appropriate (request maternal also)	Reducing substances, sulfites, organic and amino acids, alpha aminoadipic semialdehyde (AASA)
Cerebrospinal fluid	Paired (plasma and CSF) glucose Cell counts and differential Glucose and total protein HSV 1/2 PCR Gram stain and culture *Consider save sample for future	Lactate, amino acids, neurotransmitter profile, Enterovirus PCR
Neurophysiology/ neuroimaging	aEEG (also known as CFM, if available) Continuous EEG Cranial ultrasound MRI (rarely acute)	MR spectroscopy, angiography and venography

Neuroimaging

Cranial ultrasound may identify large intracranial haemorrhages or significant congenital abnormalities. MRI may be helpful in diagnosis and prognosis[16]. Where intracranial **haemorrhage is suspected, CT scanning may be preferred** to MRI but should be discussed with the neonatal consultant and consultant radiologist before undertaking.

Generally, unless there is a clear cause and prognosis, or scanning is specifically indicated earlier, MRI is recommended at 7-14 days. For seizures associated with HIE, MR imaging is recommended at Day 5[17].

6. Monitoring of seizures

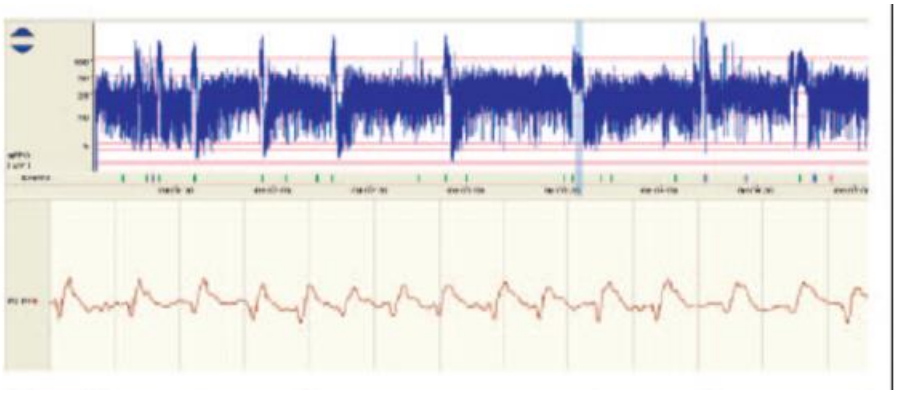
6.1 Clinical

Clinical suspicion of seizure as described previously in section 4.3 and recording them on a seizure chart (See Appendix 6).

6.2 Amplitude integrated EEG (aEEG; Cerebral Function Monitor CFM, if available on your local unit and if trained to use/interpret)

aEEG should be commenced if seizure disorder is suspected in a term/ near term infant, particularly if at significant risk (e.g. following intrapartum hypoxia) and muscle relaxed. Interpretation in pre-term infants is challenging and use is therefore not recommended outside tertiary settings.

Most electrographic seizures on aEEG are characterized as an **abrupt, transient, sharp rise in the lower margin**, often accompanied by a **smaller rise in the upper margin**, with narrowing of the bandwidth[18] as shown below, for more examples please (See Appendix 5)



Status epilepticus on aEEG is depicted as frequent, recurrent seizures giving a saw tooth appearance. It is defined as **>30 minutes or >50% of the recording, or both.** Continuous seizure activity or brief inter-ictal periods between seizures can be mistaken as normal.

Artefacts commonly mistaken for seizures on aEEG include mechanical ventilation, arousal patterns, patient manipulation, sucking or chewing and electrode artefacts. Notation of **any intervention with baby should be recorded**. Reviewing the corresponding raw EEG is essential to confirm seizures seen on aEEG[18].

6.3 EEG

EEG is usually unhelpful in acute control of seizures (use aEEG if available on your local unit). A formal EEG may be useful in confirming seizure activity in the presence of subtle neurological signs and for assessing control in infants under heavy sedation.

7. Treatment:

There is no high level evidence on the threshold for starting treatment of seizures and is limited to expert opinion[19,20]. Due to the high frequency of EEG-only seizures, continuous aEEG or EEG monitoring should be commenced if seizures are suspected (if this is available on your local unit), ideally commenced before anticonvulsants are administered (unless the infant is cardiorespiratory compromised by the seizure). Many anticonvulsants will alter the background electrical activity making neurophysiological assessments challenging[21]. See **Figure 2 Treatment algorithm.**

Firstly: Supportive management

- Airway, Breathing, Circulation

Consider and treat any reversible underlying causes, for example:

- Is the blood glucose normal? Follow local guideline for treatment of hypoglycaemia.
- Is bacterial infection or meningitis likely? Follow local infection guideline.
- Is blood chemistry normal? Treat any significant electrolyte disturbance.

Secondly: treat the seizures if:

- A single isolated seizure **lasts >3 mins** or >**3 per hour**
- Treat seizures associated with cardiorespiratory compromise

If trained in using and interpreting aEEG (CFM), **you may consider** treating subclinical (electrical only) seizures on aEEG (CFM) to reduce seizure burden. This may be associated with better short term outcomes[22,23] but should anticonvulsants are not ithout significant potential adverse effects. **Treatment of subclinical seizures should therefore only occur after consultant level discussion.**

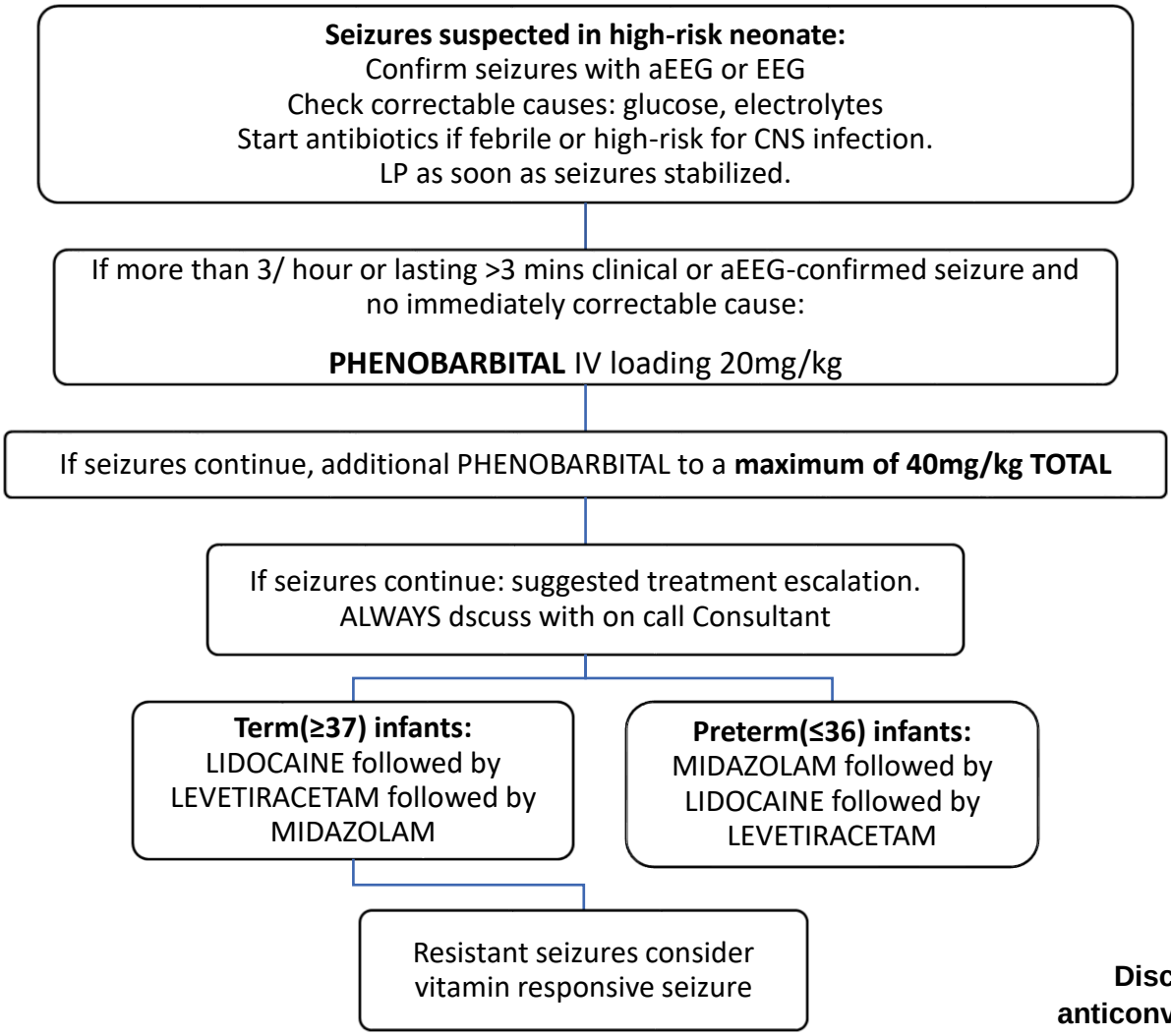
Escalating anti-seizure treatment should always be discussed with the tertiary Neonatal Consultant at each step or by a bespoke agreed plan.

Suggested treatment sequences are:

- **In full term (≥37weeks) infants: Lignocaine, Levetiracetam then Midazolam** to avoid the suppressive effects on aEEG and respiratory drive of midazolam.

- **In preterm infants: Midazolam, Lignocaine, then Levetiracetam** for superior effect of midazolam over lignocaine in preterm infants.

Figure 2: Treatment algorithm for confirmed neonatal seizures:



Discontinuation of anticonvulsants:

Most seizures in the neonatal period are Acute Symptomatic and seizure burden is finite; greatest soon after injury, hence anticonvulsant medication should be discontinued after the seizures have stopped and the neurological examination has normalised or is normalising[24]. If the seizures are suspected to be due to a neonatal epilepsy syndrome, this should be managed in conjunction with tertiary paediatric neurologists.

Vitamin-responsive epilepsies:

Investigations for vitamin-responsive epilepsies and a therapeutic trial of vitamins should be given for refractory neonatal seizures where no other cause has been identified in conjunction with tertiary paediatric neurologists. Pyridoxine **may cause apnoea or cerebral depression in those with pyridoxine dependant seizures**[25] **especially if they have received anticonvulsants**, therefore careful observation is required.

Table 5: Recommended doses for vitamin-responsive epilepsy in neonates[25–27]

Drug	Dose
Biotin	5mg orally/NGT twice a day, can increase up to 10mg twice a day

Follinic acid (Calcium folinate)	5mg orally/NGT twice a day
Pyridoxine	100mg intravenous trial dose repeated every 10 min to a max of 500mg If positive, can be given orally 15mg/kg/day in divided doses to a maximum of 500mg)
Pyridoxal phosphate	Surtees[28]: 10mg/kg/dose 2 hr apart orally as trial Baxter: 50mg/kg/day in divided doses for 2 weeks

8. Outcomes and Prognosis:

There is a low risk of seizure recurrence after early discontinuation of anticonvulsant medication in the neonatal period. Seizures often signify babies at increased risk of dying (approximately 15% mortality) or surviving with neurological impairment, developmental delay or later epilepsy (approximately 30%). The strongest predictors of outcome remain the underlying cause of the seizure, together with the background electroencephalographic activity.

Prognosis should only be determined after careful consideration of all the available information following investigation of the underlying cause[29].

9. Follow up:

Infants who develop seizures should be followed up and have a neurodevelopmental assessment performed. Other specialties may be involved, this is dependent on the underlying cause and response to treatment.

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Appendix 1:

Different seizure types, ictal electroencephalographic patterns, and clinical associations[9]

Types of seizure	Ictal EEG correlate	Clinical association
Clonic (focal, segmentary or bilateral)	Repetitive spikes	Various, frequent in neonatal stroke and other structural brain abnormalities
Myoclonic (erratic, fragmentary or generalized)	May be prominent or completely absent	Metabolic or diffuse structural disorders
Tonic (resembles decerebrate rigidity or decorticate posture)	May be prominent or completely absent or rhythmic delta activity	Most often structural brain abnormalities, sometimes also metabolic disorders
Subtle (nystagmus, blinking, tonic eye deviations, pedalling, chewing / sucking movements; apnoea, vasomotor changes)	Sometimes flattening, may be normal, follow-up EEGs recommended	Various, frequent in hypoxic-ischaemic encephalopathy

Appendix 2:

Key general physical examination findings for newborns with suspected seizures[15]

Physical Examination	Diagnostic considerations based on findings
Head circumference	• Macrocephaly- Hydrocephalus or hemimegalencephaly • Microcephaly- Congenital CNS infections (esp TORCH infections) or congenital CNS lesions
Skin/cutaneous examination	• Vesicular lesions – consider HSV infection • Vesicular lesions in a dermatomal pattern- Incontinentia pigmenti • Port wine stain of forehead/eyelid- consider Sturge-Weber syndrome and evaluate for glaucoma • Nevus or discoloration in a dermatomal or whorled pattern- developmental cerebral dysgenesis • “Blueberry muffin” skin appearance- congenital Rubella infection (or other TORCH infections) • Ash leaf macule- tuberous sclerosis • Cutis aplasia (lack of hair and skin in a localized area)- associated developmental cerebral dysgenesis
Ophthalmological examination	• Hypoplastic optic nerves – cerebral dysgenesis (e.g. septo-optic dysplasia) • Chorioretinitis – congenital CNS infections • Abnormal retinal pigmentation- neuronal ceroid lipofuscinosis • Coloboma- agenesis of corpus callosum • Congenital cataract- congenital CNS infection (esp TORCH) or metabolic (storage) disorders
Facial (or other) dysmorphism	• Hypotelorism, cleft lip/palate (mid-face abnormalities)- cerebral dysgenesis (e.g. holoprosencephaly) • Multiple congenital anomalies- chromosomal abnormalities (Trisomy syndromes, partial deletions/duplications)
Mental status	• Irritable, jittery- neonatal encephalopathy (e.g. due to HIE, neonatal abstinence syndrome, pyridoxine dependant seizures) • Lethargy, decreased responsiveness- neonatal encephalopathy (e.g. due to HIE); severe systemic illness and/or infection (e.g. meningoencephalitis)

Appendix 3:

Factors determining outcome in neonatal seizures[30]

Factors associated with poor outcomes are:

- Prematurity
- HIE
- Cerebral dysgenesis
- Central nervous system infection
- Severe IVH
- Severe abnormal EEG inter-ictal activity (isoelectric pattern, paroxysmal, burst-suppression and low-voltage background)
- Less strongly associated:
    - Severely abnormal neurological examination (less specific)
    - Severely abnormal neuroimaging
    - Early onset of seizures (within 24hrs; related to HIE in term babies)
    - Severity of seizures/presence of status epilepticus

Factors associated with favourable outcomes are:

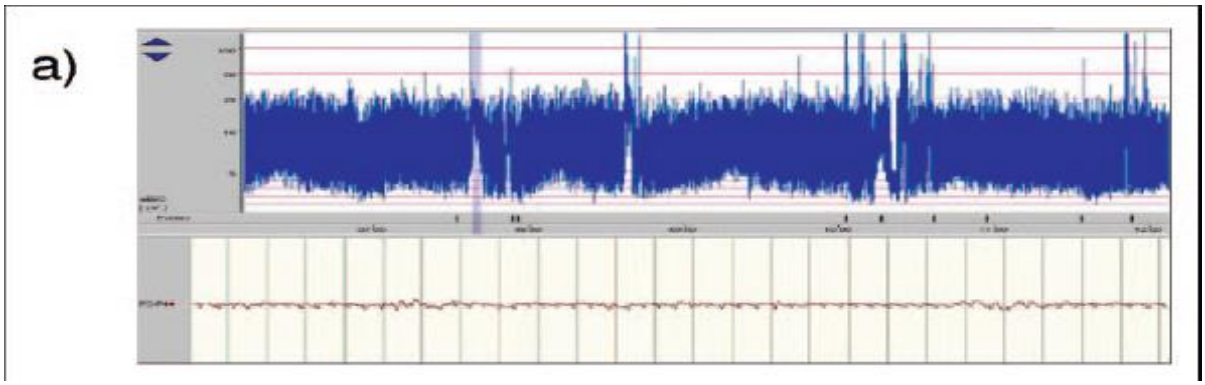
- Focal infarct ('stroke') on MRI
- Transient metabolic disturbance e.g. hypocalcaemia
- Normal inter-ictal EEG activity
- Normal early neurological examination
- Diagnosis of benign familial seizures
- Neonatal sleep myoclonus
- Clinical seizures with no EEG correlate
- Less strongly associated:
    - Normal/mild abnormality on neuroimaging
    - Late onset (>5 days; related to benign neonatal seizures)
    - Focal clonic seizures, likely related to focal structural lesion in the brain

Appendix 4: Inborn errors of metabolism manifesting with seizures[10]

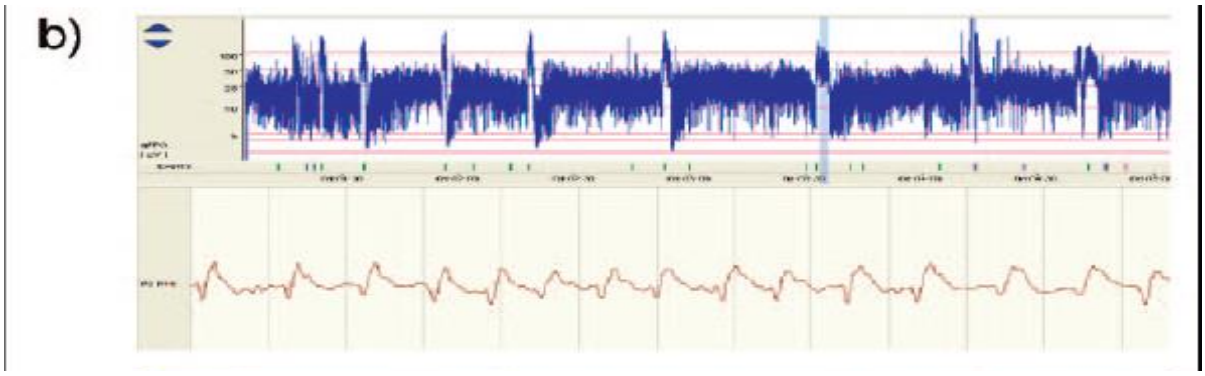
A number of IEM may present in the neonatal period:

Mechanism of seizure generation	**Aetiology**
Energy deficiency	Hypoglycaemia, glucose transporter-1 deficiency, respiratory chain deficiency, pyruvate dehydrogenase deficiency, Krebs cycle defects, creatine deficiencies
Toxic effect	Aminoacidopathies, organic acidurias, urea cycle defects, molybdenum cofactor deficiency, sulphite oxidase deficiency
Impaired neuronal function	Storage disorders
Disturbance of neurotransmitter systems	Non-ketotic hyperglycinaemia, atypical phenylketonuria, gamma aminobutyric acid (GABA) transaminase deficiency, succinic semialdehyde dehydrogenase deficiency
Associated brain malformations	Peroxisomal disorders (Zellweger syndrome), respiratory chain deficiency, pyruvate dehydrogenase deficiency, O-glycosylation defects (congenital muscular dystrophies
Vitamin or cofactor dependency, vitamin transporter defects	Biotinidase deficiency, pyridoxine-dependent and pyridoxal 5'-phosphate dependent epilepsy (follinic-acid-responsive seizures), thiamine transporter deficiency, Menkes' disease, folate transporter defect, dihydrofolate reductase deficiency
Miscellaneous	Serine biosynthesis deficiency

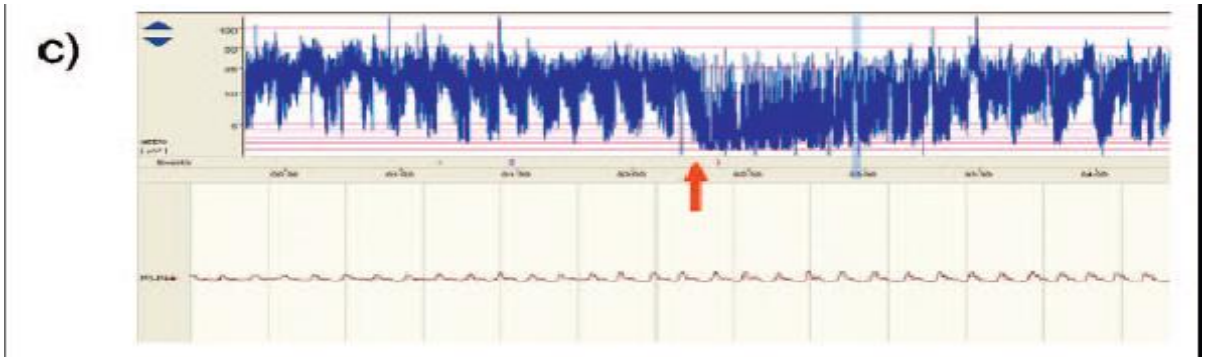
Appendix 5: Seizures on aEEG and corresponding cEEG



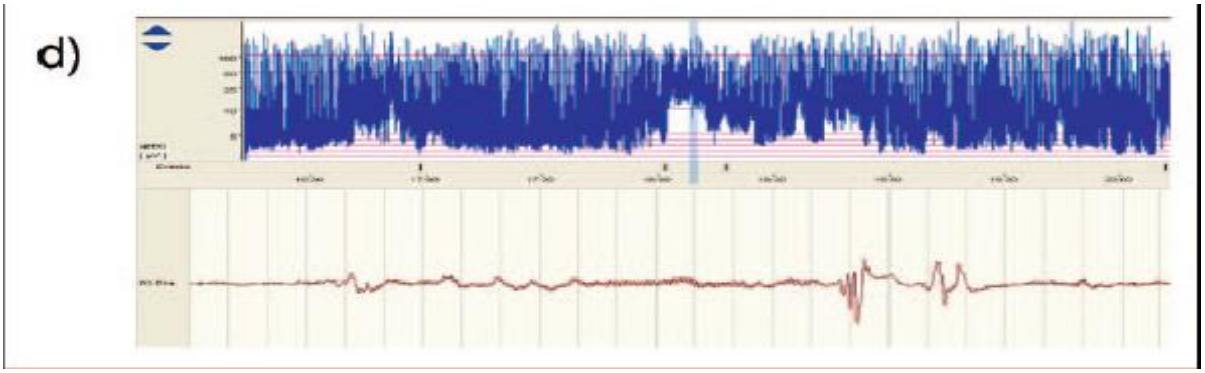
6.1: a) Three single seizures, each lasting for 2 to 4 minutes and appearing at 1- to 1.5-hour intervals on a discontinuous background. Twenty-five seconds of EEG corresponds with the first seizure. The left margin of the blue vertical bar in the aEEG corresponds with the displayed EEG.



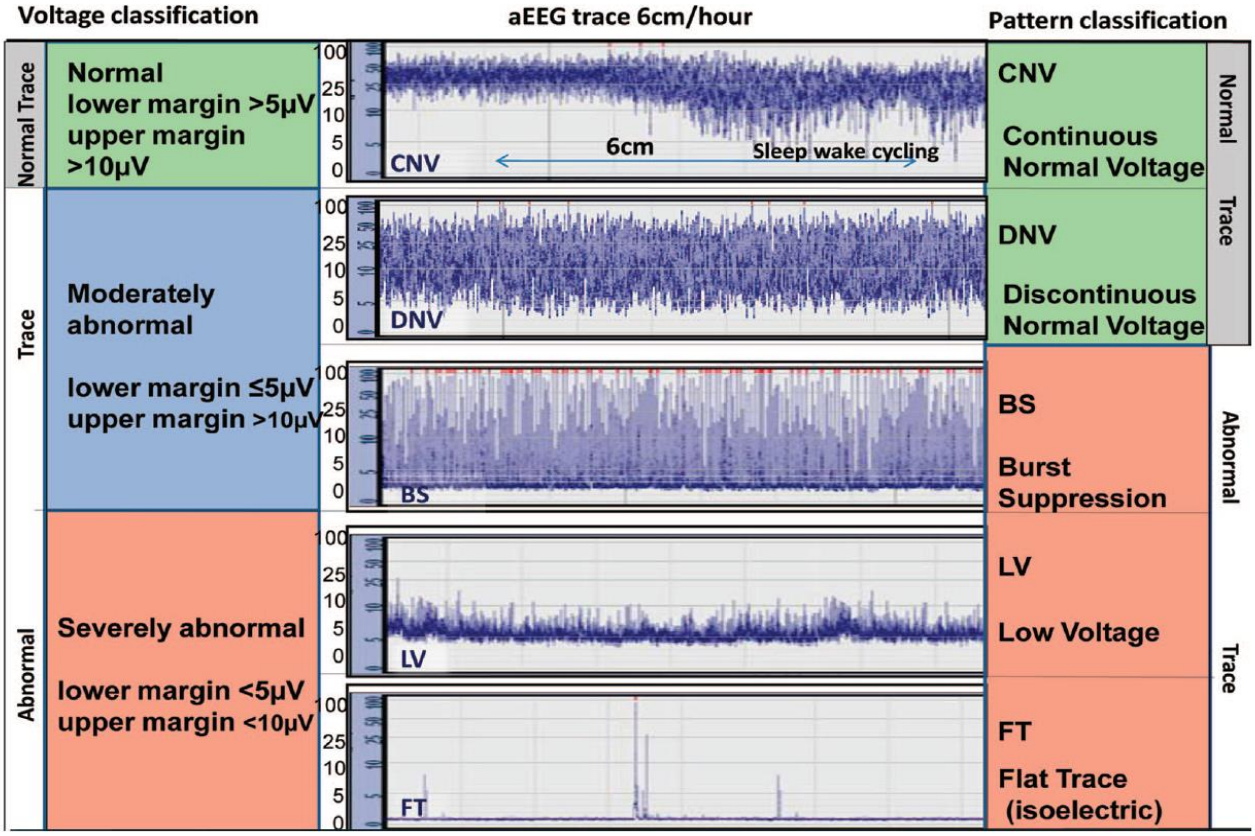
b) Repetitive seizures with 10- to 35-minute intervals on a continuous background aEEG. The 12-second EEG display is from the seventh seizure (counting from left) with the blue vertical bar.



c) Status epilepticus (“saw-tooth pattern”) after perinatal asphyxia. Administration of midazolam (red arrow) results in temporary depression of seizures and background activity. The blue vertical bar in the aEEG corresponds with the 12 seconds of EEG.



d) This is not a seizure pattern! High-frequency oscillation ventilation resulted in a very variable and raised minimum aEEG amplitude and clearly visible high-frequency interference in the EEG. The 25 seconds of EEG shows the aEEG at the blue vertical bar in this 4-hour aEEG recording. The discontinuous background in this extremely preterm infant is still possible to appreciate, but seizure activity, if present, probably would be missed. The risk of interference from mechanical ventilation on the aEEG is reduced if care is taken that electrodes are not pressed against bedding[31]**.**



6.2: Classifications of 5 example traces by using the pattern recognition method (right) and voltage method (left) to assess the aEEG background at 3 to 6 hours of age[32].

Appendix 6: **Neonatal Seizure Chart**

ADDRESSOGRAPH

NAME:

DOB:

HOSPITAL NUMBER:

Neonatal seizures can be subtle or episodes of clinically stereotyped movements which do not settle with passive restraint of the affected limb and which are accompanied by autonomic disturbances. Subtle seizures could include cycling, chewing or eye deviation. Seizures may have CFM or EEG correlate so please apply the CFAM if seizures are suspected.

Date	Time	Abnormal movement description	Duration	Autonomic changes (HR, BP, SaO2)	Response to passive restraint	CFM appearance	Comments (treatment effects etc.)
