NCCU CLINICAL GUIDELINES

SECTION: 15

NEUROLOGY

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Neonatal seizures
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NEONATAL SEIZURES

Seizures occur in the neonatal period more frequently than in any other time in life. Neonatal seizures are defined as those occurring in the first 28 days of life in a term infant or up to 44 weeks of corrected age in a preterm infant.

Seizures may be epileptiform or non-epileptiform and may have motor, behavioural or autonomic manifestations. The increased susceptibility of the neonatal brain to develop seizures is attributed to the rapid growth and changes occurring at this stage and the numerous potential insults to the brain that the neonate is exposed to. The immaturity of the brain is thought to be responsible for the types of seizures seen.

Basic mechanisms of the seizures and the capacity of clinical / electrographic seizures to produce brain damage is still being determined. What to treat and what not to remains unclear. Current practice is to treat recurrent or prolonged clinical seizures with AEDs where a specific treatable cause is not known. While phenobarbitone, phenytoin and benzodiazepines are often accepted as first, second and third line drugs for acute management, the ideal sequence and their relative efficacies are open to question.

The role of neuroprotective agents to minimize morbidity is being considered. Determining the prenatal, intranatal and post natal factors involved in the causal pathways for neonatal seizures may help identify preventable causes and tailor specific interventions to improve the associated morbidity and mortality.

AETIOLOGY

1. Hypoxic Ischaemic Encephalopathy (antepartum and intrapartum) is probably the single most common cause accounting for approximately 30% of the seizures. HIE seizures typically occur on the first day, often starting 4 – 24 hours after birth. Seizures may be difficult to control. Electrolyte abnormalities, low sugars and multisystem dysfunction may coexist. Localised ischaemic events may result in focal clonic seizures.
2. Intracranial haemorrhages are thought to be responsible for around 15% of seizures. Subarachnoid haemorrhages classically present with seizures on the 2nd day of life in a term infant and Intraventricular haemorrhages are more frequently seen in preterm infants. Subdural and intracerebral bleeds may also result in seizures.
3. Intracranial infections – viral, bacterial are seen in about 10% of infants with seizures.
4. Brain Malformations such as lissencephaly, pachygyria, cortical dysplasias account for some of the neonatal seizures.
5. Metabolic causes: may be primarily responsible for the seizures or may be contributory. Abnormalities in glucose, electrolytes including Ca, Mg, Na should be looked for. Rarely inborn errors of metabolism such as non-ketotic hyperglycinemia, urea cycle disorders, organic

acidaemias, glucose transporter enzyme deficiency etc. may be responsible. Pyridoxine deficiency or dependency is much publicised but quite rare cause of neonatal seizures. Folinic acid responsive seizures are one of the more recently discovered entities.

6. Drug Withdrawal Seizures – should always be considered and a good maternal history elicited.
7. Benign Familial Neonatal Seizures is an Autosomal Dominant condition, linked to chromosome 20 in some families, may be heterogenous, that presents with seizures in the newborn period. These seizures occur mainly between 1-7 days (up to 3 weeks) and unless very frequent do not need treatment with AEDs. Long-term ~ 15% with BFNC develop epilepsy.
8. Another interesting benign neonatal condition of unknown pathology, whose incidence appears to be declining, is Fifth Day Fits. This is not a familial condition. A single Australian study suggested it was associated with Zinc deficiency, a finding not reproduced in other studies. Seizures in this entity are usually clonic or apnoeic, recur and disappear in a few days without sequelae.

EEG

Neonates may have electrographic (EEG) seizures with and without clinical events. All neonatal seizures were previously thought to be generated by an epileptic mechanism - a hypersynchronous paroxysmal neuronal discharge in the brain. However video EEG studies have shown that some events (such as tonic posturing elicited by stimulation, with temporal and spatial summation, that can be stopped by repositioning or restraint) that meet clinical criteria for seizures are not associated with any electrographic seizures. These are now considered to be release phenomenon (disinhibition of brain stem centers by forebrain depression).

The EEG can play a very useful role in neonatal seizures. The background may help prognosticate for neurodevelopmental outcome, the EEG may offer clues to aetiology and may be the only way of detection of seizures and monitoring of response to therapy in a paralysed ventilated baby. Electrographic seizures in a neonate are extremely variable in voltage, frequency, amplitude, and polarity and may vary within the same seizure. Video EEG studies and clinical observation with EEGs have shown that a large number of electrographic (EEG) seizures may not have any clinical correlates. The significance of electrographic seizures and electroclinical dissociation is a much debated issue.

CLINICAL CLASSIFICATION OF SEIZURES

Clinically it is often useful to record whether seizures are:

SUBTLE (MORE COMMON IN THE PREMATURE INFANT)

- Abnormal behaviour, autonomic or motor manifestations that do not fall into the other classifications.
- Ocular – deviation of the eyes, staring episodes, eyelid fluttering or repetitive blinking.
- Facial – repetitive sucking, mouthing, drooling, chewing, tongue protrusion.
- Limbs – bicycling, boxing, stepping movements.
- Autonomic – apnoea, tachycardia, hypertension, pupil changes, increased salivation.

CLONIC (RHYTHMIC JERKS THAT DO NOT STOP WITH GENTLE RESTRAINT)

- Focal - 1-3 secs 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 or of trunk or neck.
- Multifocal or Generalised – extension of lower limbs with either upper limb extension or upper limb flexion.

The duration of seizures should be recorded. Most neonatal seizures occur frequently. 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.

INVESTIGATIONS OF NEONATAL SEIZURES

- Full Blood Count, Urea Electrolytes Creatinine, Blood Sugar, Ca, Mg, and LFTs.
- Head Ultrasound.
- EEG.
- Where appropriate:
- Septic screen.
- Drug screen.
- Urine Metabolic screen.
- Plasma AminoAcids.
- Serum lactate, pyruvate,
- Acid/Base status.
- CSF for metabolic studies & infectious aetiology.
- Coagulation profile and trombophilia screen
- Further neuroimaging with CAT Scan or MRI.
- Despite appropriate investigations in some neonates a cause may not be identified.

TREATMENT

1. Acute treatment and minimization of seizures in conjunction with correction of metabolic derangements. Adverse effects with Anti-Epileptic Drug (AED) Therapy may occur and therefore close monitoring is required. CNS depression, respiratory depression, hypotension, bradycardia are some of the side effects seen especially with phenobarbitone and benzodiazepines whereas cardiac events such as arrythmias, hypotension may complicate phenytoin administration.
    - Phenobarbitone is universally accepted as first line therapy. Dose – 20mg/kg/IV loading dose (with optional additional doses of 10mg/kg each up to a total load of 40mg/kg.)
    - Phenytoin is usually the second drug administered if Phenobarb alone does not work. The loading dose of Phenytoin is 20mg/kg, administered by slow infusion. 30% may be uncontrollable with these first line treatment.
    - Midazolam (benzodiazepine) infusion may be used in the acute phrase if first line therapies have not worked or are contraindicated (e.g. Phenytoin and cardiac arrhythmia's). Midazolam is becoming increasingly popular and appears to abolish most clinical seizures and up to 2/3 of electrographic seizures.

2. If abnormal metabolic profile - Correct Hypoglycaemia, hypocalcaemia, hypomagnesemia. Give Pyridoxine if deficient.

3. Infections - Treat with appropriate antiviral/antibacterial/antifungal therapy. In some instances the aetiology may be multifactorial and sometimes AED's may be necessary in addition to specific therapy.

4. Minimization of side effects of AED - Optimal duration of therapy remains undetermined. If loading doses of AED adequate, or if a specific cause has been identified and treated, there is no need to continue with maintenance therapy. However if neurological examination is abnormal at one week of age, or there has been difficulty in initial control of seizures then it would be wise to continue for a few weeks and then reassess. Under these circumstances "A two week period of no seizures" is often used (rule of thumb) prior to discontinuing AEDs. Even in those children who later develop epilepsy there is often a so-called "honey moon" period of being seizure free. The decision regarding duration of therapy has to be individualised for e.g. if a brain malformation is the cause of recurrent neonatal seizures, then long term AED therapy would be appropriate. Alternative AED's:
    - Clonazepam may be given in single doses and repeated 8 – 12 hourly if efficacious.
    - Lidocaine infusion (caution – has narrow therapeutic range)
    - Paraldehyde
    - Valproate, Carbamazepine, Vigabatrin have also been used.

PROGNOSIS

Prognosis is variable and is often dependant on the underlying cause e.g. severe HIE or lissencephaly – is associated with a poor outcome. Sequelae occur in ~30% of infants with seizures. The major sequelae seen are – Cerebral Palsy, Intellectual Disability, Epilepsy and Failure to Thrive. Mortality in neonates with clinical seizures is ~15% and possibly higher in those with electrographic seizures without clinical correlates. A normal neurological examination at one week is reassuring for a normal neurodevelopmental outcome. The EEG background is very useful for prognostication, especially on serial EEGs.

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