Management of Neonatal Seizures

The incidence of neonatal seizures in term babies is 0.1-0.3% live births and up to 1-13% in preterms. Hypoxic-ischemic encephalopathy is the most common cause in term infants, but other causes include infection, intracranial haemorrhage/infarction, metabolic abnormalities, CNS malformations and drug withdrawal.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
<td>30-55%</td>
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<tr>
<td>Intraventricular haemorrhage</td>
<td>7-17%</td>
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<tr>
<td>Cerebral infection</td>
<td>0-17%</td>
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<tr>
<td>Cerebral malformations</td>
<td>3-17%</td>
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<tr>
<td>Meningitis/sepsis</td>
<td>2-14%</td>
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<tr>
<td>Metabolic</td>
<td></td>
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<tr>
<td>Hypoglycaemia</td>
<td>0.1-2%</td>
</tr>
<tr>
<td>Hypocalcaemia/hypomagnesaemia</td>
<td>4-22%</td>
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<tr>
<td>Hyper/hypomagnesaemia</td>
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<tr>
<td>Inborn errors of metabolism (such as pyridoxine dependency, folate acid-responsive seizures, glucose transporter defect, non-ketotic hyperglycaemia, phosphopenic acidosis)</td>
<td>3-4%</td>
</tr>
<tr>
<td>Kernicterus</td>
<td>1%</td>
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<tr>
<td>Meningal drug withdrawal</td>
<td>4%</td>
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<tr>
<td>Idiopathic</td>
<td>25%</td>
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<tr>
<td>Genetic/idiopathic neonatal seizures</td>
<td>17%</td>
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<tr>
<td>Neonatal epileptic syndromes</td>
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<tr>
<td>Congenital infections</td>
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The clinical manifestations of neonatal seizures differ from those in older children. Neonates cannot sustain synchronised, well organised generalised seizures. Jitteriness is not a seizure but is frequently confused with one and may be a sign of cerebral irritation.

It is important to obtain a careful antenatal, perinatal, postnatal and family history and perform a full physical examination. A detailed description of the seizures should be documented in the notes.

Investigations should include:
1) Blood glucose
2) FBC, CRP and PCV
3) Blood gas including lactate
4) Urea, creatinine and electrolytes including magnesium, calcium, phosphate and LFTs
5) Blood culture
6) Lumbar puncture for M&C & Protein, sugar
   - If enough sample left, labs will send it to molecular lab and stored for 6 days
7) Cranial ultrasound
8) Cerebral function monitoring
9) Consider further investigations depending on clinical situation:
   a) Blood for PCR or viral load
   b) CSF specimens for virology (Check if CSF already sent)
   c) Urine for CMV PCR/HSV PCR
   d) A throat swab for a full viral screen
   e) Stool for enterovirus PCR,
   f) Metabolic screen (NH\textsubscript{3}, lactate, pyruvate, urine for organic and amino-acids, plasma amino-acids)
   g) TORCH screen - A current blood sample from the mother for CMV/toxoplasma/rubella antibody testing (information on where mum’s antenatal sample was kept)
10) EEG may assist in confirming diagnosis. The inter-ictal EEG may be useful in estimating prognosis particularly in HIE. However it is not necessary to defer therapy until an EEG can be obtained
11) CT/MRI can be diagnostic

Indications for Treatment:

- Seizures may indicate the presence of a potentially treatable aetiology
- Aetiology-specific therapy is critical since it may prevent further brain damage
- Untreated seizures may continue for extended periods of time and interfere with ventilation or precipitate cardiovascular collapse. This may impair cerebral vascular auto regulation and predispose to secondary brain injury
- In general, if seizures are frequent (>3/60min), prolonged (>3 min) or associated with cardiorespiratory compromise (frequent apneas & bradycardia, needing intervention), treatment is required

Management:
1) Ensure that ventilation and perfusion are adequate, ABC
2) Correct hypoglycemia and other electrolyte abnormalities if present:

<table>
<thead>
<tr>
<th>Hypoglycemia:</th>
<th>see separate hypoglycaemia guideline</th>
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<tbody>
<tr>
<td>Hypocalcaemia:</td>
<td>0.5ml/kg 10% calcium gluconate over 10-30 minutes</td>
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<tr>
<td>Hypomagnesaemia:</td>
<td>0.4mmol/kg Mg\textsuperscript{2+} (100mg/kg magnesium sulphate) IV over at least 10 minutes</td>
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</table>
3) Consider starting IV antibiotics +/- Acyclovir
4) Anticonvulsant treatment
5) Consider Paediatric Neurology input

**Anticonvulsant treatment:** In general there is paucity of evidence for the use of anticonvulsant therapy. (Discuss with on call consultant)

**First drug of choice**

**Phenobarbitone:**
- **a)** 20mg/kg loading dose as slow IV infusion over 30mins
- **b)** Do not exceed 1mg/kg/minute
- Levels to be taken 2 hrs post-loading dose (Aim for plasma level around 30 µg/ml)
- If the initial loading dose is ineffective, additional doses of 10mg/kg can be given until either seizures have ceased or a total dose of 40mg/kg has been achieved
- **b)** Maintenance dose 5 mg/kg day in 2 divided doses.
- Not all patients that require loading will require maintenance treatment. Will depend on the severity of seizures.

**Second line drugs include:**
1) **Levetiracetam (Keppra):**
- **a)** Loading dose 30 mg/kg and then
- **b)** Maintenance of 30mg/kg/day in 2 divided doses.
2) **Midazolam:**
- **a)** 150-200 micrograms/kg as a slow IV push over 5 min
- **b)** Continuous infusion at 1mcg/kg/min, increased by 1mcg/kg/min every 15 minutes to a maximum of 5 mcg/kg/min for persistent seizures.
3) **Clonazepam:** may be given as a single loading dose or as a loading dose followed by an infusion
   - **a)** Loading dose: 100 microgram/kg IV over at least 30 seconds
   - **b)** Continuous infusion: 10 mcg/kg/hour, adjusting according to response to a maximum of 40 mcg/kg/hour.
4) If there are recurrent seizures with no obvious cause eg HIE or hemorrhage, consider pyridoxine deficiency/dependency early. A therapeutic trial of **Pyridoxine** IV 50-100 mg may be helpful. This should be done during EEG monitoring.

Other drugs may be helpful eg **Topiramate** currently being used increasingly in pediatric practice. **Phenytoin** may be useful in the acute setting especially if given intravenously. Please discuss with Pediatric neurology if seizures require more than 2 antiepileptic drugs to control.

Duration of therapy and use of maintenance treatment will depend on the individual case. The aim is to discontinue AEDs as soon as possible; if this is not possible aim for monotherapy. The drug used most commonly is Phenobarbitone 3 - 5mg/kg/day. If discharged home on anti-epileptic treatment, drug levels will need to be monitored at the earliest opportunity.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading dose</th>
<th>Maintenance</th>
<th>Half life</th>
<th>Side effects</th>
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</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>20mg/kg - 40mg/kg IV</td>
<td>5mg/kg/day in 2 divided doses IV/PO</td>
<td>50-140 hrs</td>
<td>Respiratory depression, drowsiness, irritability (Ataxia &amp; Nystagmus in toxicity)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>30mg/kg IV</td>
<td>30mg/kg/day in 2 divided doses IV/PO</td>
<td>6-8 hrs</td>
<td>Drowsiness, ataxia, irritability</td>
</tr>
<tr>
<td>Midazolam</td>
<td>150-200µg/kg IV over 5 min</td>
<td>1µg/kg/min increased by 1µg/kg/min every 15min Max : 5µg/kg/min</td>
<td>6-8 hrs</td>
<td>Hypotension, reduced cardiac output, apnoea &amp; respiratory depression, seizures with rapid IV bolus</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>100µg/kg IV</td>
<td>10-40 µg/ kg/hr IV</td>
<td>1-3 hrs</td>
<td>Hypotension, reduced cardiac output, apnea &amp; respiratory depression, seizures with rapid IV bolus</td>
</tr>
</tbody>
</table>

**Prognosis:**
The neurodevelopmental outcome depends on the cause and severity of seizures. It is important that all infants with neonatal seizures have follow-up arranged following discharge from the Neonatal Unit.

**References:**
4. Neonatal Seizures E-Medicine article
5. Anticonvulsants for neonatal seizures. Booth D, Evans DJ. *Cochrane Systemic review2004*

Dr. Deepa Vineet and Dr Sybil Barr November 2013 to be reviewed November 2016.