Neonatal seizures

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Neonatal seizures are common and may be the first manifestations of neurological dysfunction after a variety of insults. Neonatal seizures are clinically significant because very few are idiopathic. Further investigation leading to prompt diagnosis of the underlying condition is important because many of the aetiologies have specific treatments which, when used early, may improve the prognosis.

Neonatal seizures cause further neuronal compromise, but it is not clear whether this leads to further clinically significant neuronal injury in all, or even many seizures. Many of the clinical studies examining outcome associated with seizure activity have been confounded by the prognosis associated with the underlying aetiology. It is also unclear if adverse neurodevelopmental outcome, occurring as a consequence of seizures, can be prevented by current treatment. Many clinicians are therefore uncertain when to treat seizures and how to assess the adequacy of treatment.

The immature brain seems more prone to seizures; these are more common in the neonatal period than during any other time throughout life. This may reflect the earlier development of excitatory synapses, predominating over inhibitory influences at early stages of maturation. The incidence of clinical seizures in infants born at term is 0.7–2.7 per 1000 live births. The incidence is higher in preterm infants, ranging from 57.5 to 132 per 1000 live births (<1500 g birthweight). The incidence of electrographic, clinically silent seizures is unknown. Continuous EEG monitoring of infants after one clinical seizure showed that 79% of subsequent EEG seizures were clinically silent. Such phenomena seem to be more common in preterm infants.

There are four recognisable clinical seizure types: subtle; clonic; tonic; and myoclonic. Each can be focal, multifocal (involves more than one site, is asynchronous, and often migratory), and generalised (diffusely bilateral, synchronous, and non-migratory). Table 1 summarises the main features of the seizure types.

### Types of clinical seizure

A clinical seizure is a sudden, paroxysmal depolarisation of a group of neurones that results in a transient alteration in neurological state. This may involve abnormal motor, sensory, or autonomic activity, with or without a change in conscious level. A seizure may arise from varying foci at different times. Not all clinical seizures are correlated with EEG changes and not all seizures shown on EEG recordings are clinically apparent, for reasons discussed below.

Neonatal seizures differ in clinical description from those in adults, and seizures in preterm infants differ from those in term infants. Cerebral cortical organisation, synaptogenesis, and myelination of cortical effert pathways are poorly developed in human neonates, leading to weakly propagated, fragmentary seizures whose electrical activity may not spread to surface EEG electrodes. The more advanced development within the limbic system with connections to mid-brain and brain stem may explain the higher frequency of mouthing, eye deviation, and apnoea in neonates than seizures in adults. Thus the clinical manifestations can be extremely inconspicuous in neonates.

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### PAROXYSMAL, NON-CONVULSIVE PHENOMENA

It may be difficult to distinguish some of the less discernible neonatal seizures from other

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**Table 1** Types of clinical seizures (adapted from Volpe 1989)*

<table>
<thead>
<tr>
<th>Type</th>
<th>Term Relative frequency</th>
<th>Preterm Relative frequency</th>
<th>Clinical manifestation</th>
<th>Associated EEG activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtle</td>
<td>54%</td>
<td>48%</td>
<td>Eyelid fluttering, eye deviation, fixed open stare; chewing, sucking, tongue thrusting, cycling, boxing, pedalling limb movements; tachycardia, unstable blood pressure; apnoea (Variable)</td>
<td></td>
</tr>
<tr>
<td>Clonic</td>
<td>23%</td>
<td>32%</td>
<td>Rhythmic jerking (1-4/s), consciousness usually preserved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Focal:</strong> Limbs or one side of face or body; may suggest underlying focal lesion such as cerebral artery infarction but can be due to metabolic disturbance +</td>
<td></td>
</tr>
<tr>
<td>Myoclonic</td>
<td>18%</td>
<td>13%</td>
<td>Rapid, isolated jerks (distinguish from benign neonatal myoclonus)</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Generalised:</strong> Extension of upper + lower limbs accompanied by pronation of arms and clenching fists -</td>
<td></td>
</tr>
<tr>
<td>Tonic</td>
<td>5%</td>
<td>7%</td>
<td><strong>Focal:</strong> Sustained posturing of limb (rare) +</td>
<td>-</td>
</tr>
</tbody>
</table>
paroxysmal episodes occurring in the newborn that are non-convulsive in origin. Apnoea can be a manifestation of a subtle seizure although most apnoeic episodes in preterm infants do not represent seizure activity. Such non-convulsive apnoea is usually associated with a bradycardia. Convulsive apnoea, associated with EEG seizure activity, is more likely in term infants, particularly if the apnoea is not accompanied by bradycardia but is associated with other subtle phenomena, such as eye opening, fixed staring, deviation of eyes. Jitteriness is a common benign neonatal movement disorder characterised by symmetrical tremor of the extremities, sparing the face. The movements are of equal rate and amplitude (clonic and myoclonic seizures have fast and slow components), occurring at a higher frequency than clonic movements (5–6 per second). Jitteriness is generally induced by an external stimulus and ceases with gentle restraint or passive flexion. It occurs in infants without neurological impairment and is not necessarily an abnormal feature. The most commonly identified causes are hypoxic–ischaemic encephalopathy, hypoglycaemia, hypocalcaemia and drug withdrawal.

### Major causes of neonatal seizures

Many pathologies can give rise to a neonatal seizure (table 2), although only a few of these conditions account for most seizures. Very few neonatal seizures are idiopathic (2–5%).

#### Hypoxia–Ischaemia

Hypoxic–ischaemic (HIE) insults ("asphyxia") account for about 50% of cases of neonatal seizures. Most asphyxiated infants with seizures have a moderate degree of encephalopathy presenting with subtle, focal, or multifocal fragmentary clonic seizures, usually within the first 24 hours. Myoclonic and tonic seizures can occur in the most severe form of HIE and can be difficult to control pharmacologically. Other insults such as hypoglycaemia, hypocalcaemia, and subarachnoid haemorrhage may coexist and trigger postasphyxial seizures.

#### Central Nervous System Infection

Seizures may be the first presentation of a bacterial meningitis, underlining the importance of performing a lumbar puncture after a neonatal seizure. The most commonly isolated pathogens are group B *Streptococcus*, *Escherichia coli*, *Listeria sp*, *Staphylococcus* and *Pseudomonas* species. Further investigations may be required if other CNS infections are suspected, such as, for example, herpes simplex encephalitis, intrathecal infections.

#### Intracranial Haemorrhage

Subdural and subarachnoid haemorrhage can occur in term infants following birth trauma and may cause seizures independently of any associated asphyxial insult. In preterm infants severe intraventricular haemorrhage, with or without associated parenchymal venous infarction, can be followed within a few hours by generalised tonic seizures. Isolated germinal matrix haemorrhages are unlikely to produce seizures.

#### Cerebral Artery Infarction

In infants presenting with seizures, whose Apgar score was normal and subsequent investigations failed to reveal an infective or metabolic aetiology, a high percentage of ischaemic lesions were demonstrated by early magnetic resonance imaging before changes on cranial ultrasound scan became apparent.

#### Acute Metabolic Disturbance

Hypoglycaemia is the cause of convulsions in only 3% of cases, although it occurs frequently in infants with seizures because it coexists with other causes, such as hypoxia–ischaemia, infection, etc. The definition of hypoglycaemia is also debated. The level constituting a risk of neurological impairment is variable, depending on the metabolic state of the infant. Nevertheless, when faced with a convulsing infant whose blood glucose is below 2.6 mmol/l, most clinicians would advocate correction of the perceived hypoglycaemia.

Hypocalcaemia presents typically either within the first 3 days of life or later in the neonatal period. Early onset hypocalcaemia occurs in infants of diabetic mothers, low birthweight infants, after exchange transfusion but, like hypoglycaemia, can also occur in association with other aetiologies, particularly hypoxia–ischaemia. Thus early onset hypocalcaemia is also often associated with neonatal seizures, although it is the sole cause in only about 3%. Late onset hypocalcaemic convulsions are now rare. The incidence of late onset hypocalcaemia has fallen following the introduction of low phosphate milk formula.

#### Less Common Causes

Inborn errors of metabolism are a rare cause of neonatal seizures and should be considered when seizures are unresponsive to conventional treatment in neonates with a positive family history.

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**Table 2. Aetiology of neonatal seizures**

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Percentage contribution %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia-ischaemia (&quot;asphyxia&quot;)</td>
<td>46</td>
</tr>
<tr>
<td>CNS infection</td>
<td>17</td>
</tr>
<tr>
<td>Meningitis, encephalitis, intraventricle infections</td>
<td>10</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>10</td>
</tr>
<tr>
<td>Extraventricular, subdural, subarachnoid haemorrhage, periventricular haemorrhage (PVH)</td>
<td>6</td>
</tr>
<tr>
<td>Cerebral artery infarction</td>
<td>6</td>
</tr>
<tr>
<td>Acute metabolic disturbance</td>
<td>5</td>
</tr>
<tr>
<td>Hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyper or hyponatraemia (or rapidly changing sodium)</td>
<td>4</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>4</td>
</tr>
<tr>
<td>Aminoacidurias, urea cycle defects, organic acidopathies, peroxisomal disorders, pyridoxine dependency</td>
<td>4</td>
</tr>
<tr>
<td>CNS malformation</td>
<td>4</td>
</tr>
<tr>
<td>Maternal drug intoxication</td>
<td>4</td>
</tr>
<tr>
<td>Cocaine, heroin, methadone, etc</td>
<td>4</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>4</td>
</tr>
<tr>
<td>Benign neonatal seizures</td>
<td>4</td>
</tr>
<tr>
<td>Benign familial neonatal convulsions (BFNC)</td>
<td>4</td>
</tr>
<tr>
<td>Benign idiopathic neonatal convulsions (BINC, &quot;fifth day fits&quot;)</td>
<td>4</td>
</tr>
<tr>
<td>Benign neonatal sleep myoclonus</td>
<td>4</td>
</tr>
<tr>
<td>Neonatal epileptic syndromes</td>
<td>4</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4</td>
</tr>
</tbody>
</table>
history, recent introduction of milk, acidosis, or distinctive odour.

Pyridoxine dependency is a rare defect in an enzyme involved in production of the inhibitory neurotransmitter GABA (autosomal recessive) and presents with early onset intractable seizures. The EEG may show generalised bursts of bilaterally synchronous high voltage 1–4 Hz activity with interspersed spikes,15 but the diagnosis is established by observing cessation of seizures within minutes of administering 50–100 mg pyridoxine (normalisation of the EEG may be more gradual).

Neonatal drug withdrawal is a common cause of neurological signs—for example, jitteriness, diarrhoea and autonomic dysfunction—although only about 5% will include seizures, usually within the first three days. Drugs misused by the mother responsible for such signs are usually narcotic analgesics, barbiturates, cocaine and alcohol. Methadone related neonatal withdrawal seizures can occur any time up to 3 weeks of life.17 Cocaine misuse may predispose to prenatal cerebral artery infarction which may cause seizures.

Benign familial neonatal convulsions (BFNC) represent a self limiting (within 1–6 months) autosomal dominant syndrome presenting with clonic seizures on the second or third day. The infant has no abnormal neurological signs in the interictal period, investigation reveals no apparent cause, and subsequent development is usually normal.

Benign idiopathic neonatal convulsions (BINC or “fifth day fits”) describe multifocal clonic seizures, the peak time of onset of which is the fifth day, generally ceasing within 15 days. The cause is unknown, although low cerebrospinal fluid zinc concentrations have been described in some cases.18 Very few cases have been reported recently. The term “fifth day fits” probably represents a meaningless diagnosis and should be avoided.

Benign neonatal sleep myoclonus consists of bilateral, synchronous myoclonic jerks occurring during quiet sleep. Onset is within the first week and resolves within two months. The EEG shows no abnormal activity between or during these episodes. Neurological outcome is normal.

Two rare syndromes, early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy (EIEE), characteristically present in the first weeks with severe recurrent seizures and are associated with inborn errors of metabolism (EME) and structural CNS abnormalities (EIEE).19 Both lead to severe subsequent neurodevelopmental impairment. During the neonatal period the seizures are fragmentary myoclonic and clonic in EME, and tonic in EIEE, both showing a burst-suppression EEG pattern.

Investigations

DETERMINATION OF THE AETIOLOGY

The large differential diagnosis following a neonatal seizure (table 2) demands that any investigations should be undertaken in a logical sequence. Certain clues to the aetiology may be present, such as a history of perinatal asphyxia or maternal narcotic abuse, but other causes such as hypoglycaemia, hypocalcaemia, and CNS infection may coexist and need excluding. The initial investigations should concentrate on the common aetiologies that require prompt specific treatment. Table 3 lists the required investigations and the suggested sequence.

IMAGING

Cranial ultrasound scanning is readily available in most centres and is useful as a first line imaging investigation for exclusion of gross CNS pathology—CNS malformations, periventricular haemorrhage—but it may fail to detect other forms of clinically important pathology, such as cerebral arterial infarction, subdural and subarachnoid haemorrhage. If the initial ultrasound examination is normal but the infant continues to have seizures or has abnormal interictal neurological signs, a computed tomogram or MRI examination should be carried out.

ELECTROENCEPHALOGRAM (EEG)

The EEG can provide confirmation that any observed neurological phenomena are seizures. However, not all clinical seizures are detected by EEG, particularly certain subtle seizures, most generalised tonic seizures, and the focal and multifocal myoclonic seizures. Two explanations have been proposed. The first is that some seizures may originate at a subcortical level (myoclonic) and are not propagated to surface electrodes because of the immature synaptogenesis and cortical projections.20 The other is that subtle and generalised tonic seizures are not, in fact, epileptic—that is, due to CNS hypersynchronous electrical discharge—but are primitive brain stem and spinal motor patterns released from tonic inhibition normally exerted by the forebrain.21

Continuous EEG recording is recommended for infants who are paralysed, to detect the frequency and duration of seizures. Unfortunately access to routine EEG monitoring is very limited in most clinical settings and the interpretation is very observer dependent, requiring considerable experience. This greatly reduces the value of this technique. A more convenient form of continuously monitoring seizure and background activity is to use the modified amplitude integrated EEG or cerebral function monitor (CFM).22 Cerebral
activity is recorded from three electrodes and printed out on a compressed time scale at the cot side. Seizures can be recognised by a period of higher voltage activity with a narrow range of voltages, compared with background activity. CFM output needs to be interpreted with caution as artefacts, such as movement, will be erroneously recorded as cerebral activity, transient disturbances may be overlooked because of the compressed time scale, and low frequency seizures may be filtered. Any form of continuous monitoring will also detect clinically silent seizures in non-paralysed infants, particularly preterm infants, which are of uncertain clinical importance.

Interictal background EEG abnormalities are helpful in determining prognosis in both term and preterm infants. A poor prognosis is associated with burst–suppression and persistent low voltage states, although experience is required when assessing EEGs of preterm infants, as these normally show discontinuous activity with long interburst intervals.

Treatment
Two principles exist. The first is to detect and treat the underlying cause of the seizure, paying particular attention to associated acute metabolic disturbances, such as hypoglycaemia. The second principle is the assessment of the need to control the seizures, which involves balancing the benefits of stopping some or all of the seizures against any potential deleterious effects of anticonvulsant medication. It is this second principle that provokes the greatest debate.

Several mechanisms exist whereby neuronal compromise could occur during seizures. These have been elucidated from studying induced, and often prolonged, seizures in animal models and from neurophysiological observation of neonates.

Hypoventilation during a seizure leads to hypoxia and hypercapnia; these are usually accompanied by an increase in arterial blood pressure. Increased cerebral blood flow has been observed during prolonged seizures in animals using magnetic resonance spectroscopy (31P-MRS) and is correlated with the rise in systemic arterial pressure, suggesting loss of cerebrovascular autoregulation. A regional increase in cerebral blood flow, corresponding to the site of electrical activity in a neonatal focal seizure, has been shown with positron emission tomography, and increased Doppler cerebral blood flow velocities have been observed in other neonatal seizures.

Repeated neuronal membrane depolarisation during a seizure necessitates increased ion pumping and consequently increased ATP consumption. This depletion in intracellular energy status is reflected by a decrease in the phosphocreatine to inorganic phosphate ratio (PCr:Pi) and can be observed by 31P-MRS. This energy failure allows further depolarisation, promoting further seizure activity, and may lead to seizure induced neuronal necrosis. The consumption of ATP and production of ADP also stimulates glucose utilisation, producing a lactic acidosis.

Glutamate is an excitatory neurotransmitter that is released after depolarisation. The post synaptic re-uptake mechanisms are energy dependent and may therefore be impaired, leading to an excessive glutamate activity during the seizure. In animal models this results in harmful elevation of neuronal calcium concentrations, leading to further glutamate release and subsequent cell death. The pattern of seizure related neuronal death corresponds to the distribution of glutamate receptor expression.

Seizures themselves can therefore cause further neuronal compromise, but it is unclear how important these mechanisms are in the clinical situation. Several questions have yet to be answered. How long must a seizure occur before permanent CNS injury ensues? How does the degree of compromise vary with the type of seizure, such as clinically silent EEG seizures? What is the capacity of the neonate to recover from such transient compromise? How does the capacity for recovery and repair depend on CNS maturity and gestational age?

If it is assumed that seizures are detrimental, how aggressively should they be controlled and do the benefits of using anticonvulsants outweigh the side effects?

Seizure Control
Prolonged or poorly controlled neonatal seizures have been associated with worse outcome than infrequent or readily controlled seizures, but the severity of the underlying disorder may account for both poor seizure control and adverse outcome. There are no clinical data which show that anticonvulsant treatment alters neurodevelopmental outcome when controlled for the underlying neurological disorder. Many of the commonly used anticonvulsant regimens are ineffective in controlling all seizures, clinically or electrically. Abnormal EEG activity still persists in a significant proportion of neonates who show a clinical response.

It is probably wise to attempt to control frequent or prolonged seizures, particularly if causing disturbance to ventilation and blood pressure homeostasis. Our practice is to use anticonvulsants if there are three seizures per hour or more, if any one seizure lasts for three minutes or more (table 4). After clinical seizure control persisting EEG seizures are rarely treated, as they tend to be brief and fragmentary; further treatment increases the risk of side effects. Many of the anticonvulsants cause respiratory depression and impair myocardial function. Therefore, respiratory activity and blood pressure should be monitored, as respiratory support and treatment of hypotension may be required.

Anticonvulsants
Many drugs have been used in the management of neonatal seizures. Table 4 summaries our approach to anticonvulsant treatment.

Phenobarbitone is the most popular first line anticonvulsant. An initial intravenous loading dose of 20 mg/kg achieves clinical control in
40% of neonatal seizures, increasing to 70% when further 10 mg/kg doses are administered to a final loading dose of 40 mg/kg (approximate serum concentration 180 mmol/l).37 The maintenance dose is 6 mg/kg/day, given 12 hourly in divided doses (therapeutic range 90–180 mmol/l). The half life (3–8 days) is prolonged in hepatic impairment. As well as its anticonvulsant activity, phenobarbitone decreases CNS metabolic rate at high dose, reduces calcium entry after ischaemia, and is a free radical scavenger. Long term use in animals inhibits brain growth and abnormal development.

Of the second line drugs, clonazepam may be used with a loading dose of 100–200 mg/kg, followed by infusion at 10–30 mg/kg/hour if seizures continue. Other benzodiazepines are also popular. Lorazepam has been used successfully, although it may induce myoclonus in low birthweight infants. Diazepam has an extremely short duration of action with a risk of sudden respiratory depression and its use should be avoided.

Phenytoin can be a useful addition to achieve seizure control. We use a loading dose of 20 mg/kg but do not continue further treatment because of its depressive effect on the neonatal myocardium and its unpredictable metabolism.

There has been recent interest in using lignocaine, a class Ia anti-arrhythmic agent, which is thought to suppress seizures through inhibition of sodium entry. A loading dose of 2 mg/kg, followed by infusion of 6 mg/kg/hour, was effective in treating neonatal seizures refractory to phenobarbitone. Prolonged infusion may result in accumulation of metabolites and may be responsible for cases of repeated seizures on withdrawal. Clearance is reduced in preterm infants and monitoring of plasma concentrations may be advisable (therapeutic range 3–6 mg/l). Lignocaine should not be used together with phenytoin as serious cardiac arrhythmias can develop.

Paraldehyde can be a useful adjunct. It has a relatively short half life (12–24 hours); elimination is by hepatic metabolism and pulmonary transport and is unaffected by altered renal function. Reported side effects include hepatic necrosis and pulmonary oedema. A loading dose of 200–400 mg/kg can be given rectally or intravenously, followed by an infusion of 15–150 mg/kg/hour to achieve seizure control (0.3–3 ml/kg/hour of a 5% solution, made up in 5% dextrose). Plastic syringes need to be changed every 12 hours and the solution should be protected from light.

Sodium valproate has been used to treat intractable seizures, using an oral loading dose of 20 mg/kg, followed by 10 mg/kg/12 hourly. There is a wide variation in plasma clearance, necessitating monitoring of drug concentrations (therapeutic range 185–425 mmol/l). There are concerns about hepatotoxic effects. In the series reported hyperammonaemia was observed in all cases; half resolved spontaneously and half resolved after withdrawal of the drug.

An infusion of chlormethiazole has occasionally been used to control intractable seizures, although there is little published evidence to support its use.

In individual clinical cases each additional anticonvulsant used should prompt a critical reappraisal of the need for further treatment, as side effects may be potentiated by multiple anticonvulsants.

The possible adverse effects on the developing CNS of continuing anticonvulsant treatment for several months have raised concern. This prompted a Swedish study to evaluate the risk of seizure recurrence following a policy of early anticonvulsant withdrawal once seizures were controlled and subsequent EEGs did not show recurrent seizures or multiformal epileptiform activity. Only three of 36 surviving infants (8%) had recurrent seizures within a year (one was discharged from the neonatal unit on anticonvulsants). Our recommendation is to withdraw anticonvulsant treatment once seizures are controlled and the neurological examination is normal. In most cases, this can be achieved prior to discharge from the neonatal unit.

**Prognosis**

The prognosis is determined primarily by aetiology. The prognosis following isolated
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hypocalcaemia or benign familial neonatal seizures is excellent. Early hypocalcaemia, CNS infections, and hypoxia–ischaemia have an adverse intermediate prognosis (30–50% normal), while CNS malformations are generally associated with a poor neurodevelopmental outcome.

Seizure characteristics associated with adverse outcome are generalised myoclonic or tonic seizures, intractable seizures, and burst-suppression or persistent low voltage EEG states. A normal interictal EEG is associated with a good outcome. Other clinical factors associated with poor outcomes are persisting neurological abnormalities on clinical examination and very low birthweight. Only 25% of infants less than 31 weeks of gestation had a normal outcome after EEG confirmed seizures, compared with 60% of term infants.

Children with neonatal seizures but who subsequently were considered to have a normal outcome were followed up in their late teenage years and found to have difficulties with spelling, arithmetic and memory, despite having normal overall intelligence. This suggests that the underlying CNS vulnerability which contributes to neonatal seizures may be of longer term clinical importance.