Recognition and management of neonatal seizures
Malcolm Levene

Abstract
Seizures are the most common major manifestation of central nervous system dysfunction in the newborn. There are many causes, but perinatal asphyxia and haemorrhagic/infarction lesions account for about 75%. There is now considerable evidence that frequent but short seizures in the neonate affect subsequent neurodevelopmental outcome. Studies using EEG or modified continuous tracing of EEG activity (aEEG or CFM) have shown that there is often electroconvulsive dissociation. This refers to poor correlation between electrical seizures and clinical seizures. Commonly used anticonvulsants appear to increase electroconvulsive dissociation. Effective management of neonatal seizures has proved very disappointing and less than 50% of seizures are abolished by first-line anticonvulsant medication (phenobarbitone or phenytoin). Drugs such as midazolam and lidocaine may further reduce seizures but require more evaluation. The challenge is to assess new and more effective anticonvulsants which are themselves associated with little neurotoxicity.

Keywords antiepileptic drugs; EEG; neonatal seizures; neurodegeneration

Convulsions are the most common major neurological sign seen in newborn infants and their incidence estimated from large population studies is 2.6 per 1000 live births. Premature infants are over four times more likely to have convulsions than full-term infants. Neonatal status epilepticus (continuous seizure activity lasting 30 min or more) diagnosed clinically is rare and accounts for only 5% of infants with seizures, although this is now recognized more frequently as the result of continuous EEG monitoring.

Neonatal convulsions are described as presenting in a number of different ways and various seizure types can be seen in the same baby over a number of hours. The frequencies of the various patterns of seizure activity are given in Table 1. In very premature babies and to a lesser extent in term infants, minor movement abnormalities may be difficult to identify as subtle seizures. These include lip smacking, tongue thrusting, mouth-ing, pedalling type movements of the lower limbs or swimming movements of the arms. Apnoea can be a common manifestation of subtle seizures. The signs can be protean and vary from baby to baby or even in the same baby. Virtually any stereotypic movement may be a manifestation of a seizure disorder in the newborn.

Aetiology
The more carefully the fitting baby is investigated, the more likely it is that a cause for the seizures will be found. A number of recent papers have described the aetiology of neonatal convulsions after extensive investigations. Tekgul et al. recently studied a consecutive group of full-term infants with evidence of neonatal convulsions (recognized both clinically and on EEG) and reported their outcome. Table 2 summarizes these data as well as risk of moderate or severe disability for each causative factor. Perinatal asphyxia is the commonest cause for convulsions in term infants, with haemorrhagic or ischaemic lesions also being common.

Overall the prognosis for the group of term babies with convulsions was good; 72% had a favourable outcome. Where asphyxia (hypoxic–ischaemic insult) is the cause of neonatal convulsions, the outcome is poor in 50%. The prognosis for neonatal convulsions when they were due to arterial or cerebrovenous infarction or intracranial haemorrhage was generally good. Individually, inborn errors are a very rare cause of neonatal convulsions, but in view of the treatable nature of some of these it is essential that these be considered and investigated appropriately.

Malcolm Levene MD FMedSc FRCPCH FRCH is Professor and Head of Department of Paediatrics and Child Health at University of Leeds, Leeds, and Honorary Neonatologist at Leeds General Infirmary, Leeds, UK.
Controversies in the clinical management of neonatal seizures

In recent years we have learnt much more about the neurobiology of seizures and their effect on the developing brain. The neonatal brain is in a neurophysiologically hyperexcitable state compared to the more mature brain and therefore is more prone to seizure activity. This is due largely to a relative excess of GABA neurotransmitters. GABA receptors are usually inhibitory, but in the immature brain they have a paradoxically excitatory effect. This changes at about term in primates and with progressive development they adopt a neuroinhibitory role.6

The propensity to seizures in the neonatal brain makes resolving the balance of risks between continuing seizure activity on the one hand against potentially adverse effects of therapy on the other a very important equation. Added to this is the problem of accurately diagnosing neonatal seizures and whether commonly used anticonvulsants are successful in controlling them.

These conundrums can be posed as a series of challenging questions which are discussed below.

Do neonatal convulsions cause brain injury?

Convulsions are a sign of neurological compromise and may indicate significant underlying structural brain damage or biochemical disturbance which may cause further brain damage in its own right. There has been considerable debate about the scale of the disability that convulsions cause the immature brain over and above that due to the underlying cause. Most of our knowledge comes from studies in rodents and these have provided some tentative answers to this question.

Seizures in the mature brain lead to neuronal necrosis, but studies in very young rat pups, whose brain development is somewhat similar to full-term infants, have shown that a series of five brief seizures on five successive days does not cause structural neuronal damage but does produce morphological changes in hippocampal neurons and, worryingly, deficits in the rat learning and visual spatial memory function in adolescent and adult life.7 A single prolonged neonatal convolution in similarly immature rats does not produce any functional effects.8 Others have shown that following priming of the neonatal rat brain by short seizures as described above, a further insult comprising induction of status epilepticus in the same rats at an older age causes neuronal necrosis.9 This has been referred to as the ‘two hit hypothesis’.10

A more specific question is, does seizure activity in an already significantly compromised brain cause additional neuropathology? Wirrell et al.11 studied a series of immature rat pups with the induction of an hypoxic-ischaemic (asphyxial) insult followed by either chemically-induced fits or a control sham procedure. In the more severely asphyxiated animals the degree of brain damage was increased significantly in those that had the additional burden of induced seizures.

In summary, these studies show that the immature brain is more resistant to short, frequent post-seizure damage than the mature brain, but despite resulting in no loss of neuronal numbers, the function of the brain is permanently affected in later life. In the asphyxiated brain, seizures appear to have an additional adverse effect on brain damage. Furthermore, the immature brain that has been ‘primed’ by early seizures is more vulnerable to status epileptics later in life. It would appear from these data that frequent seizures in the human infant should be stopped and this begs the question as to whether currently used anticonvulsants effectively control neonatal seizures?

Can we rely on clinical versus EEG diagnosis of neonatal convulsions?

Traditionally, the diagnosis of neonatal convulsions has been made by observation and description of the frequency of abnormal movements. EEG has been technically difficult in the hostile electrical activity of a neonatal intensive care environment and considerable expertise is required for analysis of the trace. It is usually not practical to undertake traditional EEG recordings at the time the baby shows abnormal movements. More recently, various technological developments have allowed more direct investigation of neuronal electrical activity by either video-EEG or compressed recording of the amplitude integrated EEG (aEEG or CFM).

Rennie et al.3 at King’s College Hospital, London have undertaken extensive evaluation of video-EEG and have found that this technique detects many convulsions not recognized by a single channel aEEG or CFM trace. Of 19 infants with evidence of convulsions on EEG, only four were recognized on CFM, but this may have been due to the observers’ lack of experience with this technique. In other centres that have developed appropriate expertise, aEEG or CFM has proved more sensitive to the detection of seizures. Video-EEG studies have also shown that many movements interpreted by experienced clinicians to be seizures are not associated with abnormal cortical activity. Conversely, many electrical seizures are not associated with abnormal movements. This is referred to as electroconvulsive dissociation.

In summary, clinical observation alone to detect the fitting baby is unreliable in that it may either over-detect seizure activity which is not present on EEG or under-detect clinical seizures in infants with EEG-proven convulsions. The decision as to which babies to treat with antiepileptic drugs therefore becomes somewhat arbitrary.

Do anticonvulsants stop neonatal seizures?

Although neonatal seizures are common there are few randomized controlled trials assessing the benefits of antiepileptic drugs (AEDs) in the treatment of this condition. Phenobarbitone is the most widely used first-line AED and in an Australasian study 95% of neonatologists and paediatric neurologists used this drug as first-line management.12 The most commonly used loading dosage is 20 mg/kg, but regimens of up to 40 mg/kg have been recommended (Table 3).13 Four trials have evaluated the effect of phenobarbitone in abolishing neonatal seizures. Two of these studies used EEG to monitor response to the drug14,15 and one compared phenobarbitone with phenytoin.15 In the latter study seizures were completely controlled in only 43% of babies and in the group where phenytoin was the first drug used, complete seizure control was achieved in 45%. This study switched babies from their first AED to the other if complete control was not obtained on EEG monitoring after exposure to first-line therapy. In babies who had been given phenobarbitone as first-line therapy, seizure control was only achieved in 57% after phenytoin was added. In those given phenytoin first, complete
Dosage regimens for first-, second- and third-line anticonvulsants in the neonatal period

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Loading dose</th>
<th>Second loading dose if first unsuccessful</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbitone</td>
<td>20 mg/kg by slow iv injection</td>
<td>10 mg/kg iv</td>
<td>2.5–5 mg/kg od</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg iv over 20 min</td>
<td>Not recommended</td>
<td>1 μg/kg/min iv infusion, increasing to 5 μg/kg/min until favourable response</td>
</tr>
<tr>
<td>Midazolam</td>
<td>150–200 μg/kg iv infusion</td>
<td>6 mg/kg/h for 6 h iv, then 4 mg/kg/h for 12 h, then 2 mg/kg/h for 12 h</td>
<td></td>
</tr>
<tr>
<td>Lidocaine*</td>
<td>2 mg/kg iv over 10 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.05–0.1 mg/kg by slow iv injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.3–0.4 mg/kg iv over 3–5 min</td>
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*Lidocaine should not be used if the infant has previously been treated with phenytoin.

Table 3

seizure control was achieved with the adding of phenobarbitone in 62%.

Boylan et al. assessed the efficacy of phenobarbitone (20–40 mg/kg iv over 20 min) in 14 babies monitored by video-EEG: in only four was there complete abolition of seizures and in the other 10 electroconvulsive seizure activity increased whereas clinical evidence of seizures reduced. This has been termed electroclinical dissociation and anticonvulsant drug use in the newborn appears to increase this feature. They also showed that the babies least likely to respond to the first-line AED are those with the most abnormal background EEG.

Two studies have evaluated the use of phenobarbitone in babies who had sustained significant asphyxial insult at birth. Hall et al. compared high-dose phenobarbitone (mean 39 mg/kg) versus standard dose (27 mg/kg) and reported fewer convulsions and a significant reduction of severe disability or death in the high dose group (RR 0.30; CI 0.10–0.93). A recent study from India of babies with hypoxic-ischaemic encephalopathy randomized 25 babies to phenobarbitone (20 mg/kg loading dose) and compared them with 20 control babies. Only 2 of 25 (4%) in the phenobarbitone group developed convulsions compared with 8 of 20 (40%) in the control group (p = 0.01). Because of the specific enrolment criteria (asphyxial insult), neither of these studies is strictly comparable to the studies by Painter et al. and Boylan et al. whose intention was to assess the efficacy of first-line anticonvulsant therapy on convulsions of any cause diagnosed either clinically or by EEG.

Other anticonvulsants used as second- and third-line drugs have been subject to few studies in the newborn. Midazolam is administered as a bolus followed by continuous infusion. A recent study has shown that in 10 of 13 neonates given intravenous midazolam for status epilepticus control of electrical seizures was achieved within the first hour of treatment, having been previously shown to be refractory to phenobarbitone treatment. Some of these babies required a second bolus infusion of midazolam to control all electrographic seizures.

In some parts of Europe lidocaine is used as a third-line anticonvulsant. Malingre et al. evaluated 20 infants refractory to both phenobarbitone and midazolam and who were then given lidocaine by continuous infusion. Lidocaine was effective in abolishing electroconvulsive seizures diagnosed by aEEG in 76% of the treatment courses studied. No babies developed cardiac arrhythmias, a previously reported complication of lidocaine in older patients. As a result of pharmacokinetic studies the dosage regimen has been modified (see Table 3).

In summary, phenobarbitone is effective in seizure control in less than 50% of babies and even when combined with phenytoin the efficacy of these drugs together remains poor. More worrying is the observation that phenobarbitone tends to reduce clinically evident seizures, thereby giving the clinician a false sense of security whilst having little or no effect on the numbers of electroconvulsive disorders. This has been summarized appropriately as ‘after all these years, we still love what doesn’t work’. Both midazolam and lidocaine infusions appear to be effective in abolishing severe seizures in some infants resistant to phenobarbitone. Lidocaine should not be given to babies previously exposed to phenytoin for fear of a synergistic adverse effect on cardiac rhythm.

Do antiepileptic drugs cause brain damage?

A risk–benefit analysis is needed to evaluate the efficacy of anticonvulsants in stopping neonatal seizures, which is poor with standard anticonvulsants, as discussed above, against the risk of administering the anticonvulsant drugs themselves. Phenobarbitone has been reported to have adverse effects on the developing brain, including inhibition of brain growth, neuronal toxicity, and adverse behavioural and cognitive effects into adult life when administered to young animals.

Phenytoin shows unpredictable plasma levels and potential cardiotoxicity.

Recent studies have shown an effect of AED exposure on the developing brain by causing neurodegeneration. Phenytoin administration to immature rat pups at doses which produce serum levels similar to those achieved in human neonates was associated with widespread neuronal death as a result of apoptosis (programmed cell death). Phenobarbitone had a similar effect when a dosage regimen similar to 40 mg/kg was used and...
this effect was maximal in the more immature brain. Diazepam and clonazepam also resulted in a similar effect. Midazolam and lidocaine were not tested in this study. The combination of phenobarbitone or phenytoin with diazepam had a particularly profound effect on neurodegeneration.

In summary, recent data suggest that the commonly used AEDs for neonatal convulsions may in themselves cause neurodegeneration due to apoptosis, with lasting effects on development. Many babies with neonatal convulsions are treated with at least two AEDs and this may produce more severe adverse effects than the seizures themselves.

**Practical management of neonatal seizures**

Assimilation of these data and formulation of a rational policy is difficult when faced with a fitting neonate on an intensive care unit and pressure on the medical staff to ‘do something’, but it is important to accept that sometimes doing nothing is preferable to using potentially dangerous drugs in a situation which does not warrant such intervention. Many babies who have normal interseizure neurological clinical findings and whose seizures are relatively brief and infrequent probably do not need anticonvulsant medication. A normal or near-normal background EEG trace should reassure the clinician that anticonvulsants can be withheld.

Some causes of neonatal convulsions are treatable, such as meningitis, hypoglycaemia, hypocalcaemia and inborn errors of metabolism, and each baby should be rapidly and carefully investigated for cause of the convulsions.

In some babies clinical assessment of seizures is difficult, i.e. when the baby is very sick, small or paralyzed. Sometimes it may be difficult to assess the significance of certain movement patterns. Under these circumstances an EEG may prove to be very helpful. In many units EEG is not available out of hours and a simple aEEG or CFM is strongly advised. Modern instruments are very simple to apply and prolonged or frequent seizures should be identified with only moderate training. The printout can be faxed to a more senior doctor if there is doubt as to what is shown on the trace.

The balance of knowledge now is that frequent seizures cause additional damage to the developing brain and that treatment to abolish the seizures is warranted. Unfortunately, there is little evidence that the majority of seizures can be effectively terminated by current standard therapy. Furthermore, it appears that the more abnormal the background EEG the more difficult it is to control the seizures. Nevertheless a written protocol for the management of neonatal convulsions is required on each unit. Phenobarbitone and phenytoin remain the mainstay of treatment, although their effectiveness is disappointing. There is little to suggest that midazolam is more effective than lidocaine as third-line therapy, but lidocaine is precluded if phenytoin has been previously used.

In view of the anxiety as to the neurodegenerative effects on the immature brain of most anticonvulsants used in the neonatal period (particularly when multiple drugs are used), it is preferable to use only one drug to maximum dosage before introducing a second. In addition, the duration of anticonvulsants should be minimized and the drugs stopped at the earliest opportunity. It is my practice to stop anticonvulsants prior to discharge from hospital if the baby is neurologically normal on clinical examination.

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**REFERENCES**


**Practice points**

- The clinician needs to be aware that almost any repetitive, stereotype movement pattern can be a manifestation of neonatal seizures.
- EEG is important in defining neonatal seizures.
- Frequent short-lived seizures have been shown to cause long-term neurodevelopmental problems.
- Conventional anticonvulsant medication is ineffective in abolishing neonatal seizures in greater than 50% of cases.
- There is evidence that exposure of the neonatal brain to multiple anticonvulsants causes neuronal death.
- Future research is needed to evaluate more effective anticonvulsants for treating this condition.