

Neonatal seizures

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Introduction

The immature brain seems more prone to seizures than the more mature brain. Seizures are more common in the neonatal period than during any other time throughout life. Seizures in the neonatal period are also the most common neurological emergency and are associated with high mortality and morbidity^{1,2}.

The incidence of seizures in infants born at term is 0.5–3 per 1000 live births; the incidence is even higher in preterm infants, ranging from 1–13% of very low birthweight infants³. Variations of described numbers of incidence can be explained by different diagnostic definitions and methods used. Most of these epidemiological studies include only clinical seizures. The exact incidence of electrographic, clinically silent seizures is as yet unknown. The majority of neonatal seizures occur on the first day, and 70% of all cases eventually recognised have been diagnosed by the fourth day.

Aetiology

In contrast to seizures in infancy and childhood, most neonatal seizures are acute and symptomatic with suspected specific causes; relatively few seizures are idiopathic or part of a

Table 1. Causes of neonatal seizures³⁻⁵.

Cause	Frequency
Hypoxic-ischaemic encephalopathy	30–53%
Intracranial haemorrhage	7–17%
Cerebral infarction	6–17%
Cerebral malformations	3–17%
Meningitis/septicaemia	2–14%
Metabolic	
Hypoglycaemia	0.1–5%
Hypocalcaemia, hypomagnesaemia	4–22%
Hypo-/hypernatraemia	
Inborn errors of metabolism (such as pyridoxine dependency, folinic acid-responsive seizures, glucose transporter defect, non-ketotic hyperglycinaemia, propionic aciduria)	3–4%
Kernicterus	1%
Maternal drug withdrawal	4%
Idiopathic	2%
Benign idiopathic neonatal seizures	1%
Neonatal epileptic syndromes	
Congenital infections	

clearly defined epilepsy syndrome. Although many causes can give rise to neonatal seizures (Table 1), although only a few of these conditions account for most seizures. Few seizures are idiopathic. Several decades ago, late hypocalcaemia due to a low calcium:phosphate ratio in baby formula was a frequent cause of neonatal seizures but this is very rare today. At term, hypoxic ischaemic encephalopathy is the most common underlying factor, typically with onset 6–8 hours after the hypoxic insult but within the first 24 hours of life. In preterm infants, cerebrovascular events are the most common cause. Meningitis, focal cerebral infarction, metabolic disorders and congenital abnormalities of the brain can cause seizures at any gestation.

Mechanism

The developing brain is particularly susceptible to developing seizures in response to injury; several mechanisms are likely to be involved. Overall the hyperexcitable state of the immature brain is based upon enhanced excitatory neurotransmission, paucity of inhibitory mechanisms, developmental expression of neuronal ion channels, age-dependent modulation of neuropeptides and age-dependent early microglial activation. In the immature brain there is a relative excess of excitatory neurotransmitters and receptors^{6,7}. The arborisation of axons and dendritic processes as well as myelination are incomplete in the neonatal brain resulting in weakly propagated, fragmentary seizures whose electrical activity may not spread to surface EEG electrodes.

Generalised tonic-clonic seizures are rare in the first month of life and not seen in the preterm infant. Neonatal seizures are usually focal, often short lasting (see EEG, Figure 1). The development within the limbic system with connections to midbrain and brainstem is more advanced than the cerebral cortical organisation, leading to a higher frequency of mouthing, eye deviation, and apnoea in neonates than seizures in adults.

Clinical manifestation and classification

Even among trained observers, clinical neonatal seizures may be difficult to recognise and differentiate from either normal behaviours or abnormal movements of non-epileptic origin⁸. Additional problems arise when the relationship between clinical and electroencephalographic seizures is considered. At times, there is temporal overlap of the two (so-called ‘electroclinical seizures’). However, in some clinical settings up to 85% of electrographic seizures are clinically silent (i.e. only electroencephalographic seizure activity present with no clinical accompaniment, referred to as ‘electrical only seizures’), leading to significant underestimation of seizure burden⁹. For these reasons, in the broadest terms a seizure in this age group is best defined either in clinical terms as an abnormal paroxysmal event (with or without EEG seizure activity) or electrographically as a sustained epileptiform change in the EEG, which may or may not be accompanied by paroxysmal alteration in neurological function.

As aetiology and presentation of neonatal seizures is different to seizures in older children and adults, they do not easily fit into the 1981 ILAE classification of epileptic seizure types or the 1989 ILAE classification of epilepsy syndromes and epilepsies⁶². While this continues to be a widely accepted view, the most recently proposed ILAE (The International League Against Epilepsy)⁵⁵ classification suggested that neonatal seizures should not be considered a distinct seizure type, but could be classified within its more general, universal scheme – which would classify all neonatal seizures as either ‘focal seizures’ or ‘other’⁵⁵. Several classifications have been proposed, of which the classifications by Volpe³ (according to clinical features only) and by Mizrahi and Kellaway^{4,10} (according to pathophysiology: epileptic or non-epileptic origin) are more widely used (Table 2).

Table 2. Classification of neonatal seizures.

(1) adapted from Volpe³		
Type	Characterisation	Ictal EEG abnormalities
Subtle	Ocular, oral-buccal-lingual, autonomic, apnoea, limb posturing and movements	Variable
Clonic	Repetitive jerking, distinct from jittering. Unifocal or multifocal	Common
Myoclonic	Rapid isolated jerks. Focal, multifocal or generalised	Common if generalised, uncommon if focal
Tonic	Stiffening. Decerebrate posturing. Focal or generalised	Common if focal, uncommon if generalised
(2) adapted from Mizrahi and Kellaway^{4,10}		
Type	Characterisation	Epileptic origin
Focal clonic	Rhythmic muscle contractions	✓
Focal tonic	Sustained posturing of limb/trunk	✓
Myoclonic	Random single contractions	✓/-
Spasms	Flexor or extensor, ± in clusters	✓
Electrographic	By definition no clinical correlate	✓
Generalised tonic	Sustained symmetric posturing	-
Motor automatism	Ocular, oral-buccal-lingual or progression movements of limbs	-

The Mizrahi classification has the advantage that it takes the origin of events into account and includes clinically silent electrographic seizures. According to the Volpe classification seizures can be subtle, myoclonic, clonic or tonic. Subtle seizures are the most common seizure type in both preterm and term babies. Manifestations include:

- Ocular phenomena (staring, blinking, eye deviation, eye opening)
- Oral phenomena (mouthing, chewing, sucking, smiling)
- Autonomic phenomena (change in blood pressure and/or heart rate, pallor, increased salivation or secretions; central apnoea occurring rarely as the only seizure manifestation)
- Fragmentary body movements (limb posturing, swimming, pedalling).

Similar phenomena and motor behaviours occur in neonates, especially in premature infants and encephalopathic infants. Although they are often less stereotyped and may be suppressed by restraints or triggered by stimulation, these are clinically very difficult to diagnose⁵. Prolonged video-EEG has clearly shown that the majority of infants with subtle seizures will exhibit ictal rhythmic epileptiform activity^{4,11}. The absence of ictal EEG discharges makes an epileptic origin of these movements less likely. This issue has been addressed in the Mizrahi classification: motor automatisms without clonic or tonic components and without EEG correlate are not considered to be of epileptic origin.

Clonic seizures can be focal, multifocal migrating from limb to limb or, rarely, hemiconvulsive. Jacksonian march is exceptional in neonates, but may be seen in babies with stroke. These seizures are most likely to be correctly diagnosed clinically¹². However, they may be difficult to differentiate from non-epileptic movements, like jitteriness, tremors or shudders. These non-epileptic movements can be suppressed by gentle restraint and may be enhanced by sensory stimuli. There is good correlation with EEG changes.

Erratic, fragmentary or more generalised myoclonic jerks are often associated with tonic spasms, with multifocal clonic or tonic patterns, or with mixed seizure types. They may persist into infancy (infantile spasms). Myoclonic seizures can easily be distinguished from benign neonatal sleep myoclonus by the absence of myoclonia during wakefulness and a normal EEG.

Focal tonic seizures are characterised by stereotyped, abrupt or slower tonic posturing of limb, and/or trunk or eyes, often accompanied by apnoea, flushing, or mild cyanosis. The EEG background is often abnormal and ictal discharges are common. Although still considered in the Volpe seizure classification, generalised tonic posturing is unlikely to be epileptic seizures, but rather to represent transient decerebrate or decorticate posturing, which can be triggered by stimulation and show no ictal EEG correlates. EEG background activity is severely abnormal and the outcome is poor. This seizure type is not classified as being of epileptic origin in the Mizrahi classification.

A characteristic feature of neonatal seizures is the phenomenon of electro-clinical dissociation: seizures can be electroclinical, electrographic (subclinical) or clinical only¹³. The significance of clinical only seizures is unclear. There is an ongoing controversy as to whether electrical-only seizures have an impact on long-term outcome and thus require treatment or not. There is now evidence that they have a similar impact on long-term outcome as electro-clinical seizures¹⁴.

Traditionally, the ILAE has also included some neonatal epileptic syndromes in its classification⁶¹. Most recently, the ILAE proposed a revised syndromic classification that now includes: benign neonatal familial seizures, early myoclonic encephalopathy (EME), and Ohtahara syndrome (early infantile epileptic encephalopathy, EIEE)⁵⁵. These will be discussed later.

Investigations

The large differential diagnosis following a neonatal seizure (Table 2) demands that the initial investigations should concentrate on the common aetiologies requiring prompt specific treatment. 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. Investigations include:

- Septic screen, including blood cultures and lumbar puncture
- Laboratory: always glucose, electrolytes, blood gas, packed cell volume, if necessary bilirubin, ammoniac, metabolic screening, TORCH, screening for drug abuse
- Consider therapeutic trial of pyridoxine and pyridoxal phosphate
- Always cranial ultrasound scanning, consider MRI
- EEG.

Neuroimaging

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). If initial ultrasound examination is normal, but the infant continues to have seizures or has abnormal inter-ictal neurological signs, a CT or MRI examination has to be carried out to detect other forms of clinically important pathology, such as cerebral infarction, subdural and subarachnoid haemorrhage or cerebral malformations.

EEG

EEG definitions vary, but paroxysms are considered to be seizures if they last more than 10 seconds. Neonatal electrographic seizures are often not sustained. The typical duration of the electrographic neonatal seizure is 2–3 minutes¹⁵, but many seizures will be shorter, particularly in preterm infants¹⁶. In spite of this, the total seizure burden can be very significant. Neonatal seizures have a focal onset, whereas a generalised onset spike and wave seizure discharge is extremely rare. Neonates can display simultaneous independent focal electrographic seizures (Figure 1). Neonatal status is currently defined as a total seizure time occupying 50% of a recording. Abnormal background activity is associated with an increased risk of seizures^{17,56} and poor neurodevelopmental outcome.

Discharges of less than 10 seconds' duration have been termed BIRDs (brief inter-ictal rhythmic discharges or brief ictal rhythmic discharges) and are of uncertain significance. However, BIRDs have been associated with seizures in the same or subsequent EEG and with poor neurodevelopmental outcome¹⁸.

EEG can provide confirmation that any suspicious phenomena are seizures. However, not all clinically observed seizures are detected by EEG and many neonatal seizures are subclinical (electro-cortical disassociation). Two explanations have been proposed: (1) some seizures may originate at a subcortical level and are not propagated to surface electrodes because of the immature synaptogenesis and cortical projections¹⁹ and (2) some subtle and tonic seizures might not be epileptic but are primitive brain stem and spinal motor phenomena¹⁰.

Cerebral function monitoring

The cerebral function monitor (CFM) has the advantage that it is widely available, and interpretation using pattern recognition can easily be learned. However, short seizures (<30 seconds) cannot be detected, low amplitude or focal seizures are easily missed and movement artefacts are difficult to exclude and may look like seizures²⁰. Thus, in neonates CFM is prone to false-negative and false-positive errors. In particular, non-experts are prone to false negative errors and the inter-observer agreement is low^{21,22,57}.

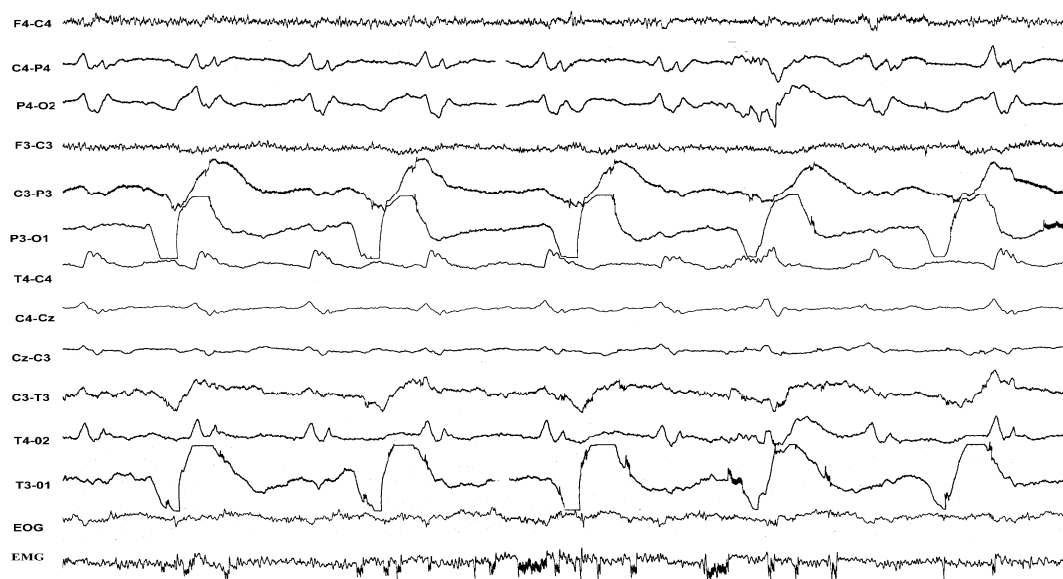


Figure 1. Characteristic features of neonatal seizures: two simultaneous, but quite different seizure pattern discharges over right and left hemispheres. There were no obvious clinical manifestations (an example of electro-clinical dissociation).

Epileptic syndromes

Benign idiopathic neonatal convulsions (fifth-day fits)

Benign idiopathic neonatal convulsions occur around the fifth day of life (day 1 to day 7, with 90% between day 4 and 6) in otherwise healthy neonates. At present the aetiology is unknown. Seizures are clonic, mostly partial and/or apnoeic²³. The inter-ictal EEG shows 'théta pointu alternant' in 60%, in the remaining neonates the background activity is either discontinuous, with focal or multifocal abnormalities, or normal. Ictal recordings show unilateral or generalised rhythmic spikes or slow-waves. Treatment may not be necessary, but the diagnosis is one of exclusion. Seizures usually resolve within days. The outcome is good, but increased risk of minor neurological impairment has been reported^{24,25}.

Benign familiar neonatal convulsions

Benign familiar neonatal convulsions constitute a rare disorder with autosomal dominant inheritance (mutations in the voltage-gated potassium channel genes: most cases 20q13.3, few families 8q24). Seizures occur mostly on the second or third day of life in otherwise healthy neonates and tend to persist longer than in benign idiopathic neonatal convulsions. They are mainly clonic, sometimes with apnoeic spells; tonic seizures have rarely been described. The background activity is normal with no specific pattern. Therapy is controversial and seizures usually resolve within weeks. The outcome is favourable, but secondary epilepsy may occur²³.

Early myoclonic encephalopathy

Early myoclonic encephalopathy²⁶ is a syndrome often associated with inborn errors of metabolism, but cerebral malformations have also been reported. Onset is nearly always in the first month of life and ictal manifestations are as follows: (1) partial or fragmented myoclonus; (2) massive myoclonias; (3) partial motor seizures; (4) tonic spasms. Background activity is abnormal consisting of complex bursts of spikes and sharp waves lasting for 1–5 seconds alternating with flat periods of 3–10 seconds in both waking and sleep. The EEG later evolves towards atypical hypsarrhythmia. Seizures are resistant to treatment, though ACTH may have some temporary effect. All infants are severely neurologically abnormal and half of them die before the age of one year.

Early infantile epileptic encephalopathy with burst-suppression pattern (Ohtahara syndrome)

Age of onset is in the first three months of life with frequent tonic spasms (100–300 per day), often in clusters²⁷. Partial motor seizures may also occur. The EEG is characterised by true burst-suppression pattern, both in sleep and waking. It may be asymmetric. During seizures desynchronisation is seen. This syndrome is usually associated with cerebral malformations, e.g. Aicardi syndrome or porencephaly. Seizures are resistant to treatment, though ACTH may have some temporary effect. The prognosis is serious, but may be somewhat better than for early myoclonic encephalopathy. Evolution into infantile spasms is common.

Both EME and Ohtahara syndrome have clinically and electrographically distinct features. However, there are also similarities, which have prompted some to suggest that they are not two syndromes, but rather part of a spectrum of a single disorder²⁶.

Inborn errors of metabolism presenting with neonatal seizures

There are also a group of metabolic disturbances, which may present as otherwise medically intractable seizures: ^{58,59}

- Pyridoxine dependency
- Pyridoxal phosphate dependency
- Folinic acid responsive seizures
- Serine deficiency

- Glucose transporter 1 deficiency
- Biotinidase deficiency
- Creatine deficiency (GAMT)
- Untreated phenylketonuria

Neonates with persistent seizures or suggestive EEG background abnormalities should all undergo a therapeutic trial with pyridoxine, pyridoxal-5-phosphate, and folic acid⁵⁸. Unexplained and persistent hypoglycaemia should be thoroughly investigated (lactate, ammonia, amino acids, urine organic acids, urine ketones, insulin, cortisol, free fatty acids, and B-hydroxybutyrate).

Glycine encephalopathy (neonatal non-ketotic hyperglycinaemia)

This inborn error of metabolism usually presents as an early myoclonic encephalopathy (see above) with seizures (myoclonus elicited by tactile and painful stimuli) on the second or third day of life. Associated respiratory distress syndrome, with periodic respiration, and coma are found. The EEG shows unusual periodic discharges on a near silent background²⁸.

Glucose transporter type 1 syndrome

Glucose transporter deficiency is a cause of seizures starting in the first three months of life, with mixed seizures types, postnatal microcephaly and encephalopathy later in the first year of life²⁹.

Pyridoxine dependency

Pyridoxine dependent seizures are a rare but treatable subgroup of neonatal seizures, which can begin in intrauterine life³⁰. Seizures of multiple types usually begin shortly after birth and are resistant to conventional antiepileptic drugs (AEDs). There may be encephalopathy and/or structural brain abnormalities. The EEG shows burst-suppression pattern, which may be interrupted by focal seizures or other generalised epileptiform activity. Pyridoxine/pyridoxine-5-phosphate is required for the synthesis of several neurotransmitters, including gamma amino butyric acid (GABA), monoamines and others. Mutations in the ALDH7A1 gene, which encodes antiquitin, were recently described in some children with pyridoxine-dependent seizures and linkage to 5q31 in some affected families. Pipecolic acid in plasma and cerebrospinal fluid is considered a possible metabolic marker for this disorder³⁰. When pyridoxine dependency is suspected, 100–200 mg of pyridoxine should be given intravenously under EEG control. The seizures will abruptly stop (within minutes) and the EEG will normalise during the next few hours. Acute suppression of EEG activity occurs occasionally and may be associated with acute cardiovascular collapse. A subgroup of affected babies responds only to very high doses given for two weeks. A closely related disorder with a similar clinical picture has now been identified as pyridoxal-5-phosphate dependent seizure.

Folic acid responsive seizures are a rare cause of neonatal seizures with clinically similar features to pyridoxine dependent seizures³⁰.

Seizures in hypoxic-ischaemic encephalopathy

Hypoxic ischaemic encephalopathy (HIE) is a common and important cause of seizure in neonates born at term. The characteristic time of onset of seizures in HIE is 8–36 hours after birth. Seizures occurring before that are usually ‘clinical only’ and are due to an abnormal increase in tone. This appears to be similar to animal studies in which the EEG activity in lambs with an intrapartum insult is at first depressed, and then evolves to show seizure activity about eight hours after birth³¹. An EEG obtained shortly after birth in which electrographic seizure activity was already manifest, would strongly suggest an insult over eight hours before delivery. Early background EEG activity is a relatively reliable prognostic indicator for outcome^{32,33}.

Treatment

Phenobarbitone remains in Europe and overseas the drug of choice in the treatment of neonates^{60,61}. The initial dose is 20 mg/kg in unventilated babies and 30 mg/kg in those who are ventilator-dependent (Table 3), aiming to achieve a serum level of 90–180 µmol/L. Phenobarbitone achieves clinical control in only 30–40% of cases³⁴; some claim better clinical control with doses of up to 40 mg/kg and serum levels above 180 µmol/L³⁵. There is, however, evidence that phenobarbitone increases the electroclinical dissociation: while the number of electroclinical seizures decreases, the number of electrographic seizures increases^{36,37}. It has been suggested that this is due to a time difference of the GABA switch which is earlier in thalamic compared to neocortical neurons³⁸.

Phenytoin and clonazepam are used as second-line AEDs. Phenytoin can cause significant myocardial depression and should be avoided in babies requiring inotropic support. Clonazepam may achieve better EEG control. Midazolam^{39,63} has a shorter half-life than clonazepam and does not accumulate, and it avoids the side effect of increased oropharyngeal secretions. Others have reported success with lignocaine^{40,63,64}: between 70% and 92% of newborns responded to lignocaine as second-line AED⁴¹⁻⁴³. However, all these studies were uncontrolled, apart from one with small numbers⁴². Lignocaine has a narrow therapeutic range and can induce seizures in high doses. There is little experience with carbamazepine, vigabatrin and lamotrigine in the neonatal period. Consider a trial of pyridoxine, pyridoxal-5-phosphate and folic acid.

A Cochrane report has reviewed the treatment of neonatal seizures⁴⁴. Only two randomised controlled studies were identified using adequate methodology^{34,42}, both indicating that current first-line treatment was only effective in about 40–50% of babies. A recent WHO review on neonatal seizures came to a similar conclusion⁴⁵. This situation has led to high usage of off-label drugs in this vulnerable age group⁴⁶, which is associated with a high risk of adverse events⁶⁵. Only recently newer AEDs have been developed and evaluated specifically for the use in the neonatal period⁶⁵. For reviews on AED treatment of neonatal seizures see van Rooij et al and Pressler and Mangum^{64,66}.

Table 3. Antiepileptic drug dose in the newborn.

Drug	Initial dose	Route	Maintenance	Route	Therapeutic level
Phenobarbitone	20–40 mg/kg	iv	3–5 mg/kg	iv/im/o	90–180 µmol/L
Phenytoin	15–20 mg/kg	iv/20 min	3–5 mg/kg	iv/o	40–80 µmol/L
Lorazepam	0.05–0.1mg/kg	iv	every 8–12 hrs	iv	
Diazepam	0.2–0.5 mg/kg	iv	every 6–8 hrs	iv	
Clonazepam	0.1 mg/kg	iv/30 min			30–100 mg/L
Midazolam	0.1–0.2 mg/kg	iv	0.1–0.3 mg/kg/h	iv	
Lignocaine	2 mg/kg	iv	1–6 mg/kg/h	iv	3–6 mg/l
Valproate	10–20 mg/kg	iv/o	20 mg/kg	o	275–350 µmol/L
Paraldehyde	0.1–0.2ml/kg	pr			
Pyridoxine (B6)	50–100mg	iv	100 mg every 10 min (up to 500 mg)		

Prognosis

This is mainly determined by the aetiology^{67,68}. The prognosis after hypocalcaemic seizures and in familial neonatal seizures is excellent. Symptomatic hypoglycaemia and meningitis have a 50% chance of sequelae in the survivors⁴⁷. In hypoxic ischaemic encephalopathy the prognosis depends very much on the grade (overall 30–50% normal), while CNS malformations are generally associated with poor outcome. Very low birthweight infants with clinical seizures have a higher incidence of impairment than preterm infants without seizures⁴⁸.

There is increasing evidence that neonatal seizures have an adverse effect on neurodevelopmental outcome, and predispose to cognitive, behavioural, or epileptic complications in later life. In animal studies, seizures impair neurogenesis and derange neuronal structure, function and connectivity leading to permanent effects on seizure susceptibility, learning and memory⁴⁹. Recent work has also shown how even a single seizure in the neonatal period may lead to long-term neuro-developmental consequences⁵⁰.

Undetected and untreated seizure activity increases the insult to the neonatal brain⁵¹. Seizures add to the hypoxic-ischaemic insult in newborn animals, and the same may be true for babies^{1,52}.

More recently a clear association between the number of electrographic seizures and subsequent mortality and morbidity has been shown¹⁴, illustrating the need for EEG monitoring in neonatal seizures.

However, there is increasing concern about the potentially adverse effects of AEDs on the developing nervous system. In animal models, phenobarbitone has been shown to cause additional brain damage by increasing neuronal death (apoptosis)^{53,54}. Better treatments for neonatal seizures have been identified as a high priority for research by several international expert groups, with emphasis on innovative strategies targeted specifically to the needs of babies with the ultimate aim to improve long-term outcome.

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