

PHENOBARBITAL (Commentary)**Recognising and classifying seizures in infancy**

Seizures are commoner in the neonatal period than at any other time of life. This is due, both to the relative excitability of the neonatal brain, and to an under-development of the inhibitory system that normally stops seizures from spreading. Fits can occur at any time, even before delivery, but are commonest in the first few days after birth. They are the outward, visible sign of an inward, invisible cerebral insult, and it is usually more important to treat the cause than its outward manifestation.

Recognition is not always easy, and the terminology used by neurologists can also be baffling. In what follows an attempt has been made to define the terms most frequently encountered. Neonatal seizures are often subtle, manifesting merely as apnoea, eye deviation, or repetitive stereotypical limb movements. As a result they can be both under- and over-diagnosed. Eye manifestations include staring, and lateral eye deviation. There may be repetitive, apparently compulsive, mouthing or chewing. Pedalling or boxing movements of the limbs also require documentation. Autonomic phenomena, such as salivation, drooling, and changes in skin colour, heart rate or blood pressure, often go unrecognised. Electroencephalographic (EEG) study is only of limited value; it can be of some prognostic significance in the semi-comatose baby, but even here other medication can make interpretation difficult. Electro-clinical dissociation is not uncommon: a "clinical" episode may be unassociated with any "electrical" discharge. The converse can also occur. Time-synchronised EEG changes are only consistently seen with clonic seizures.

Close observation is at the heart of all good nursing care, and of all reliable diagnosis. Because midwives and nurses witness seizures more often than their medical colleagues, it is vital that they should develop an ability to describe and record what they see accurately. A seizure is a paroxysm of abnormal nervous activity. It can be tonic (a generalised stiffening), clonic (a rhythmical shaking) or myoclonic (an abrupt jerk or series of jerks). It can also be focal (local) or generalised (involving the whole body). Neurologists sometimes try to further differentiate between focal and multifocal seizures. Combined tonic-clonic (also called "grand mal") seizures are not seen in the neonatal period, probably because of the brain's immaturity. Babies who look dazed or stuporose in the interval between their seizures (the inter-ictal period) have an encephalopathy.

Differential diagnosis

Jitteriness and benign neonatal sleep myoclonus can cause confusion. In jitteriness the dominant movement is tremor, unaccompanied by any autonomic change or eye movement. The tremor is easily provoked by movement, and also easily stopped by gentle restraint in flexion (unlike seizure activity). Jitteriness is of no clinical significance: it is not even a sign of hypoglycaemia. In benign neonatal sleep myoclonus limb jerks only occur when the child is going to (or waking from) sleep, do not involve the face, and resolve spontaneously (usually within 4 to 8 months). No treatment is called for. Hyperekplexia, a much rarer, dominantly inherited, non-epileptic disorder, may also present with sudden brief tonic spasms. There is hypertonia and an exaggerated startle response to unexpected noise or other stimuli (such as tapping the nose). Dangerous apnoea can occur. Clonazepam is an effective treatment. In both conditions the EEG is normal. Two other conditions associated with true seizures and an identifiable EEG abnormality can also be managed without drug treatment unless frequent seizures occur. In the genetic condition (benign familial neonatal seizures) seizures are usually first seen at 2-3 days after birth, and may continue to occur for a few months. In benign idiopathic neonatal seizures ("fifth day fits") seizures usually first present a little later and seldom persist for more than 10 days. In both conditions the baby appears alert, well and entirely normal except when fitting. A family history will help to distinguish the two conditions. About 10% of children with the former condition develop further fits in childhood requiring treatment.

Indications for anticonvulsant treatment

Many important questions about treatment cannot as yet be answered. We still do not know if poorly controlled seizures damage the brain, compromise later intelligence, or increase the chance that the child will later develop chronic epilepsy. The answer may depend on what caused the fits in the first place. The seizures seen briefly with severe jaundice ("kernicterus") are invariably associated with long term damage, but those with a low sodium or calcium are not. There is some evidence that early anticonvulsant treatment *may* improve the long term outcome of babies with an encephalopathy 12-24 hours after birth – a condition that is often caused by lack of oxygen, (and sometimes called hypoxic-ischaemic encephalopathy or HIE), but better referred to by a neutral term like "early neonatal encephalopathy" which does not presume a knowledge of its cause.

When seizures are caused by a biochemical disturbance it is usually only necessary to correct the underlying chemical abnormality. Some problems can be avoided by sensible anticipatory care. The fits caused by hypoglycaemia, hyponatraemia, hypocalcaemia and hypomagnesaemia are all eminently treatable, and never call for anticonvulsant medication. Those seen in babies with the recessively inherited abnormalities of pyridoxine or biotin metabolism respond just as rapidly once the underlying defect is recognised. Injections of lidocaine that end in the fetal scalp instead of the maternal perineum can cause seizures and a range of other symptoms that are easily confused with intrapartum asphyxia, but recovery is complete with appropriate respiratory support and there is no indication that anticonvulsant treatment improves the outcome. Restlessness can also occasionally escalate into frank seizure activity in babies born to mothers troubled by drug addiction: the logical treatment is not yet another drug but an individually tailored drug withdrawal regimen. Apnoea can sometimes be the only outward sign of seizure activity, especially in the preterm baby, but an episode of primary apnoea, if prolonged, can also precipitate an anoxic seizure if it is not terminated before severe hypoxia develops. In fits due to meningitis the only thing likely to influence the long term prognosis is the speed with which the infection is identified and treated. Once excess unconjugated bilirubin enters the brain causing kernicterus and brief seizure-like activity, irreversible damage has probably been done, and there is no evidence that any treatment is beneficial.

The case for anticonvulsant treatment is much stronger where seizures are due to underlying cerebral damage rather than a transient toxic insult. Even here, however, there is profound ignorance regarding the best way to proceed. One recent small study has suggested that the long term neurological and developmental outcome is improved by giving early high-dose phenobarbital to babies with hypoxic-ischaemic encephalopathy *before* seizures develop, rather than only starting standard medication after they do (see the monograph on phenobarbital). More such studies are urgently needed. We also need to know if such an approach has anything to offer babies with haemorrhagic lesions. Most treatment is based on the reasonable, but unproven, premise that frequent seizures are themselves damaging. Clearly seizures should not be allowed to cause recurrent hypoxia (some would consider this an indication for ventilation), and should not be allowed to interfere with nutritional intake (IV fluids must be provided if there is any risk of hypoglycaemia).

When to start treatment

While no firm consensus exists, but most clinicians would agree that –

- prolonged seizures (lasting more than about 3 minutes) should be treated,
- seizures occurring more than 2 or 3 times an hour should be treated,
- an abnormal EEG does not require treatment if the child seems normal

There is even less agreement as to whether a short-acting drug or a longer-acting drug should be given first, and very few comparative studies have yet been attempted. One logical approach is to choose a short-acting drug (such as rectal paraldehyde or lorazepam) if seizures are likely to be brief and there is little risk of recurrence (as, for example, with meningitis, periventricular haemorrhage etc.), and a longer-acting drug (such as phenobarbital or phenytoin) if there is a high risk of recurrent seizure activity (as, for example, with a cerebral malformation or severe hypoxic-ischaemic encephalopathy).

How long to continue treatment

Very little is known about the effect of prolonged anticonvulsant use on normal cerebral maturation and myelination in the first year of life. Exposure during intrauterine life is not without its long term consequences. Most babies have no further seizures if treatment is stopped as soon as the baby has had no seizures for 2-3 weeks. Where long term treatment is called for, oral carbamazepine, vigabatrin, or lamotrigine is usually effective (although the manufacturers have, as yet, only given a limited endorsement to any use of the latter two drugs in early infancy). Valproate may occasionally be appropriate, as long as there is no evidence of hepatic dysfunction or an unexplained metabolic acidosis. One concern with high dose phenytoin is the possible development of cerebellar hypoplasia.

Choice of anticonvulsant

Phenobarbital remains the most widely used neonatal anticonvulsant, but its efficacy is not as well established as is generally believed, and the best way of managing seizures that do not respond to its use remains very unclear. One problem is that treatment can sedate the baby (even to the point where mechanical respiratory support becomes necessary) and also suppress all visible muscle movement without reducing EEG evidence of continued cerebral seizure activity. This is particularly common with high dose treatment (Boylan *et al.*, 2002) and the belief that this should always be tried if standard treatment (a 20 mg/kg loading dose) fails before a second drug is given probably needs to be challenged. It has been conventional, in the past, to try phenytoin first if phenobarbital fails (or *vice versa*). The first dose of these two long-established anticonvulsants has to be large (because of the drug's wide distribution

in the body), making venous access and a slow infusion necessary. Sustained treatment with phenytoin also presents a challenge because the half life is very variable, but this is not a problem with short term use. However it now seems clear (Painter *et al.*, 1999) that only a quarter of the fits that are resistant to treatment with phenobarbital come under control when phenytoin is given too. The search for a better strategy therefore continues.

There used to be a vogue for giving diazepam if such first-line management failed, and this drug often works well in older children where fits are often relatively short lived. The policy proved less successful in neonates, possibly because the precipitating cause for any seizures often persists for some time. Because diazepam is also relatively quickly cleared from the brain, another benzodiazepine (such as clonazepam, lorazepam or midazolam) is now more often used. There is, on current evidence, little to choose between these three alternatives, and no published evaluation of neonatal use has yet been backed by consistent EEG monitoring. Benzodiazepines are strong sedatives, and there is increasing evidence that they sometimes suppress all visible muscle activity without controlling cerebral seizure activity.

Midazolam did not seem to be very good at controlling EEG evidence of seizure activity when this had already proved resistant to treatment with phenobarbital in the small randomized trial reported by Boylan *et al.* in 2004, but it did seem to be helpful in the observational study published by Castro Conde *et al.* in 2005. Further research is clearly required to address this discrepancy, but the findings will be difficult to interpret unless treatment is assigned randomly, and every child's later development is also reported. An initial disconcerting myoclonus, with or without brief cyanosis, has been reported quite often, particularly in preterm babies. There is also no doubt that first dose can, not infrequently, cause hypotension or respiratory depression in the neonatal period (Ng *et al.*, 2002). Withdrawal symptoms have been encountered with some frequency when this drug is used as a sedative for any length of time in the neonatal period. Progressive drug accumulation is also a real possibility with sustained high dose use. That few problems have been reported when these three drugs are used to control seizures, may be because it is difficult to establish whether it is the drug or the condition for which the drug is being given that is causing any symptoms seen.

The IV formulation of clonazepam and of lorazepam contains benzyl alcohol, which is toxic in excess, as does the north American formulation of midazolam. Increased secretions can be a troublesome problem with clonazepam. Many texts suggest that this benzodiazepine should always be given as a continuous infusion but it is difficult to see why this should be considered necessary given the drug's long neonatal half life. What is more, any benefit from treatment will be pointlessly delayed if a first loading dose is not given.

Thiopental is rarely used, but in one small study involving 9 babies a continuous infusion promptly controlled all abnormal EEG activity every time (Bonati *et al.*, 1990). Thiopental is a general anaesthetic making ventilatory support necessary – but many babies with intractable seizures are already on a ventilator. Unfortunately, because of drug accumulation and redistribution in the body, it takes some time for the patient to wake up after any infusion is stopped.

Paraldehyde was widely used for many years, but little written about. It causes minimal respiratory depression, does not need to be given IV as sometimes suggested (Koren *et al.*, 1988). and probably merits more formal evaluation with appropriate aEEG monitoring before other, more complex, strategies are turned to. Lidocaine use has its advocates. A 2 mg/kg IV loading dose followed by a continuous infusion of 6 mg/kg per hour controlled the seizure activity seen in 23 of 25 babies (92%) whose aEEG activity had remained abnormal despite prior treatment with phenobarbital and, on occasion, diazepam (Hellström-Westas, *et al.*, 1988). Such a dose is, however, potentially toxic if sustained for more than 12 hours (Hellström-Westas, *et al.*, 1992). There are also isolated reports that carbamazepine (Singh, *et al.*, 1996), lamotrigine (Barr *et al.*, 1999) and sodium valproate (Gall *et al.*, 1988) have benefited the occasional baby when all else failed. Valproate has to be used with great caution in young babies because there seems to be a risk of hyperammonaemia, but it certainly has a role, often on its own, in the treatment of infants with a continuing epileptic tendency.

The 'take home' message has to be that, if an attempt is to be made to control serious seizures in the neonatal period (and there is growing evidence to suggest that it should be), then it is not enough to check that visible evidence of seizure activity ceases – semi-continuous aberrant electrical activity ("status epilepticus") must cease too. One way to monitor this is to use an amplitude integrated EEG (aEEG) monitor ('cerebral function monitor'), although this does not detect all localised or short, low-voltage, seizures (Shellhaas, *et al.*, 2007).

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Use of phenobarbital during pregnancy and lactation

The use of phenobarbital before delivery is discussed in a separate web commentary that covers all anticonvulsant use during pregnancy linked to the monograph on valproate. The drug is not used in the long term control of adult epilepsy nearly as widely as it once was. Concern has often been expressed about the wisdom of use during lactation, but the clinical, as distinct from the pharmacokinetic, considerations have never received as much study as might have been expected. Given the amount found in breast milk and the drug's long neonatal half life, it is easy to predict that the blood level in the baby could well match, or even exceed, that in the mother. There have, however, been very few reports suggesting that use is actually a problem. There is one much-quoted report (Knott *et al.*, 1987) about the child of a mother on three anticonvulsants who had marked withdrawal symptoms, including EEG confirmed 'infantile spasms', when breast feeding was stopped abruptly at 7 months. Symptoms were reversed with phenobarbital and slow weaning and follow up 5 years later showed development to be entirely normal. For a few key references see:

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Febrile seizures

There is no good evidence that the prompt treatment of fever with an anticonvulsant, or with an antipyretic drug (such as ibuprofen or paracetamol), reduces the risk of further febrile seizures in a child who has already experienced at least one such event, and there is a 'trade-off' between benefit and harm with the continuous use of an anticonvulsant to reduce this risk.

Mewasingh LD. Febrile seizures. *Clin Evid* 2006;**15**:415–22 (and updates). [SR]

Managing epilepsy in later childhood

Guidance on the management of epilepsy later in infancy and during childhood has been issued by the Scottish Intercollegiate Guidelines (SIGN) Network. The National Institute for Clinical Excellence (NICE) for England and Wales have also issued guidance on the management epilepsy in children and adults. These documents are available from

- www.sign.ac.uk/pdf/sign81.pdf
- www.nice.org.uk/page.aspx?o=227586

Managing post delivery opiate withdrawal

There is now some evidence that it is worth 'covering' post-delivery opiate withdrawal with an anticonvulsant dose of phenobarbital, particularly if the mother has been using more than one illicit drug. Most of the evidence that currently exists has been summarised in the two Cochrane Reviews by David Osborne. Whether phenobarbital should be continued until the baby has been weaned off all opiate medication (Coyle *et al.*, 2002), or whether it is enough to give such treatment for the first critical few days of life remains unclear. The best opiate to use while achieving opiate withdrawal is probably methadone because of its sustained half life, and this is the easiest product to give if weaning is to be completed after discharge from hospital. However, which product is used probably matters very little. The aim has to be to minimise distress and agitation without so sedating the baby as to interfere with feeding. There is a suspicion that weaning may have been drawn out over a much longer period than was really necessary in many published studies.

While severely affected babies often show severe agitation, the proportion reported as developing fits in the many case series published to date has varied very widely. Indeed the variation is so wide that the perception as to what constitutes a true seizure is probably far from consistent.

Osborn DA, Cole MJ, Jeffery HE. Sedatives for opiate withdrawal in newborn infants (Cochrane Review). In: *The Cochrane Library*. Issue 1, 2004. Chichester, UK: John Wiley & Sons Ltd. (See also the review of opiate use.) [SR]

Coyle MG, Ferguson A, Largasse L, *et al.* Diluted tincture of opium (DTO) and phenobarbital versus DTO alone for neonatal opiate withdrawal in term infants. *J Pediatr* 2002;**140**:561–4. [RCT]

Johnson K, Gerada C, Greenough A. Treatment of neonatal abstinence syndrome. *Arch Dis Child* 2003;**88**:F2–5. [SR]

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