REVIEW

Treatment of neonatal seizures

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Newborn babies with unusual movements thought to represent seizures are usually given a loading dose of phenobarbitone without electroencephalography being performed. Antiepileptic drugs (AEDs) are then continued, with the outcome determined by clinical observation alone. AED treatment, often involving multiple drugs for long periods, is undesirable at a time when the brain is developing rapidly and likely to be especially vulnerable to any toxic effects. Despite considerable advances in the pharmacology of AEDs, continuous EEG monitoring using compact digital systems with simultaneous videorecording allowing off-line analysis, automated seizure detection, neuroimaging, and basic science research on cellular mechanisms of brain injury, treatment of such babies has progressed little. A change in practice is long overdue to allow affected babies to benefit from the advances made.

have an adverse effect on neurodevelopmental outcome and predispose to cognitive, behavioural, or epileptic complications in later life.³ In animal studies, seizures impair neurogenesis and derange neuronal structure, function and connectivity.^{4–6} Animal experiments show that seizures alter the growth of hippocampal cells, with apoptosis and “mossy fibre” sprouting of the dentate granule cells and the CA3 part of the hippocampal subfield (abnormal growth of granule cell axons). Although there is some evidence that the neonatal brain is more resistant to this kind of damage than the adult brain, the immature brain is certainly not immune to injury.⁷ The precise mechanisms and pathways by which seizures in early life exert later effects on cognition remain elusive. Intriguing evidence comes from studies in which young rats subjected to pharmacologically induced status epilepticus and then reared in an enriched environment with toys and music performed better in water maze learning tests later on than rats reared in a standard way.⁸ Similarly, rats with neonatal seizures who were deprived of maternal contact did worse than those who were reared with their dams.⁹

We and others have demonstrated that seizures are associated with an increase in cerebral blood flow velocity.^{10–11} This increase presumably reflects, but may not meet, the pathologically exaggerated demand, and any mismatch is likely to contribute to cell death and damage; undetected and untreated seizure activity certainly increases the insult to the neonatal brain of the rat.¹² Seizures add to the hypoxic-ischaemic insult in newborn animals, and the same may be true for babies.^{13–14} Status epilepticus may be particularly damaging. After kindling (brief but repetitive stimulation resulting in an accelerated and prolonged seizure effect), immature rats, like adults, have a permanent reduction in seizure threshold and are more vulnerable to damage from seizures later in life (the “two hit” hypothesis).^{15–16}

In addition to the concern that undiagnosed and untreated subclinical seizures may be damaging to the neonatal brain, new evidence is available on the cellular mechanisms of action and effects of commonly used AEDs. Many AEDs (eg phenytoin) act by modulating voltage-gated sodium or calcium ion channels, whereas others (benzodiazepines, phenobarbitone) act by enhancing the inhibition of the γ -aminobutyric acid (GABA) receptors, particularly the chloride-permeable GABA_A receptors.¹⁷ Holmes and his co-workers⁴ have shown that AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors are

Any newborn baby with unusual movements which are thought to represent seizures is usually given a loading dose of phenobarbitone without electroencephalography (EEG) being performed. The prescription of antiepileptic drugs (AEDs) is then continued, with “therapeutic success” or failure determined using clinical observation alone. AED treatment often involves multiple drugs given for a period of weeks or months, at a time when the brain is developing rapidly and likely to be especially vulnerable to any toxic effects. Investigation directed at elucidating the cause of the seizures is limited to a cranial ultrasound scan, with estimation of the blood glucose and electrolytes, occasionally including a lumbar puncture. In the four years since this topic was last reviewed for *Archives*,¹ there has been considerable progress in the field, with advances in the pharmacology of AEDs, continuous EEG monitoring using compact digital systems with simultaneous videorecording allowing off-line analysis, automated seizure detection, neuroimaging, and basic science research regarding cellular mechanisms of brain injury and the effect of AEDs. In our view a change in practice is long overdue, and babies should be among those who benefit from the advances made, not least the 10 new AEDs that have been licensed since 1990.

The notion that “what you see is what you get” is not true for the neonate with seizures. The phenomenon of electro-clinical dissociation is well recognised in this age group, and there is a very poor correlation between any electrographic signature of seizure and clinical manifestations.² There is increasing evidence that neonatal seizures

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present, but silent, in the neonate, and *N*-methyl-D-aspartate (NMDA) channels do not function at normal membrane resting potentials. Ben-Ari¹⁸ has shown that GABAergic synapses precede glutamate synapses and that receptors are formed before synapses. Many anticonvulsants work by enhancing the opening of GABA_A channels; when this channel is opened in the usual situation, negatively charged chloride flows into the neurone from the extracellular space because neurones normally have very little chloride in their cytoplasm. This “extra” negative charge means that the neuronal potential is even more negative than usual, making it less likely that the neurone will fire an action potential. Developing neurones express Na⁺/K⁺/2Cl[−] cotransporter, and this results in accumulation of intracellular chloride. Hence the neonatal neurone has a high chloride content, and consequently the developing brain has a different response to GABA (with an efflux of chloride rather than an influx), so that the response to opening of GABA_A channels is excitatory rather than inhibitory. Further, GABA_B receptors probably develop late in the neonatal period and provide little post-synaptic inhibition at this time of life. For all these reasons, “conventional” AEDs (particularly those that potentiate GABA_A receptors) are likely to prove ineffective in the newborn. Na⁺/K⁺/2Cl[−] cotransporter continues to be expressed in rat pups for up to 12 days after birth, before the chloride-exporting transporter takes over, and this explains why seizures are so refractory to treatment with AEDs that act on GABA receptors.¹⁹

In addition to providing an elegant explanation for the observation that AEDs that are effective in older children and adults do not work in the neonatal period, basic science research has also raised new questions about the safety of currently used AEDs when used in babies with rapidly developing brains. Phenobarbitone, still the most widely used first line AED in the neonatal period, has long been known to have long term effects on brain growth. Newer studies have added to these concerns, with the demonstration of increased apoptotic neurodegeneration in the developing rat brain after exposure to phenobarbitone, phenytoin, and benzodiazepines.²⁰ Valproic acid is toxic to the developing brain, as evidenced by the fetal valproate syndrome, with its attendant risks of learning and development disorders.²¹ Newer agents such as topiramate and levetiracetam look more promising in this regard, with no experimental evidence for neurotoxicity in the developing brain at anticonvulsant concentrations.^{22–23} Topiramate has the additional advantage that it may extend the window of time for which post-ischaemic therapeutic hypothermia is effective.²⁴ Recently, there has been the interesting and exciting observation that bumetanide, which is widely used as a diuretic and has a good safety profile, suppresses seizures in rat pups.¹⁹ There is increasing enthusiasm for a trial of bumetanide as an AED in the newborn.²⁵

Very few studies using EEG rather than clinical observation to measure the response to AED treatment of the newborn have been published. In one, about a third of babies responded to either phenobarbitone or phenytoin given as first line with around a further third achieving control when the other agent was added.²⁶ In our hands, midazolam was disappointing as a second line AED; babies who responded to phenobarbitone alone were more likely to have a low seizure burden and a relatively normal background EEG.²⁷ Midazolam controlled most cases of drug-resistant neonatal seizures in another study, albeit at very high doses.²⁸

In our view, the only way forward in this long neglected area is by improved access to EEG and continuous monitoring, with high quality specialised neurophysiology reporting with a rapid turn around time. The lack of specialised skills in the interpretation of neonatal EEG is inhibiting widespread use of the technique.

Given the developments in technology and the possibility of rapid transmission of large volumes of data, centralised reporting is no longer an impossible dream in the UK and could be achieved with broadband transmission to a few continuously (and properly) staffed national reporting stations. Neonatal seizures are relatively rare, and each neonatal unit would only require such a service on a few occasions each year.

The alternative is automated seizure detection, and many groups around the world (including our own) are working hard on this difficult task. As yet, no algorithm has proved robust enough to detect reliably a sufficient number of neonatal seizures to be clinically useful, probably not least because of the varied seizure morphology seen in the neonate.^{29–30} However, newly emerging signal-processing methods are constantly being applied to the important problem of automatically detecting neonatal seizures, and the problem may yet be solved. Novel approaches such as motion tracking of neonatal body movements during seizures have been described, but these methods have the major limitation that they will inevitably fail to detect subtle or subclinical seizures, which are common in babies.^{29–31} The practical problems associated with the application of multiple EEG electrodes may soon be eased by the development of disposable electrode caps designed specifically for long-term neonatal monitoring. Cerebral function monitoring is probably better than nothing, and can help with seizure recognition and monitoring of treatment in babies with a relatively normal or attenuated background EEG and high-voltage generalised seizures, but is likely to be misleading in those (particularly preterm) with moderately abnormal background EEG and low-voltage or localised seizures.³² Multichannel EEG recording with electrodes that comprehensively cover the scalp, particularly the central and temporal areas, will remain the “gold standard” for seizure recognition and have the added benefit that useful prognostic information can often be obtained from the background pattern. Large multicentre trials using continuous EEG monitoring for recognition of seizures and monitoring of therapeutic response are undoubtedly required, and could be facilitated via a centralised reporting system for neonatal EEG, which could recruit patients via the network it serviced. Such trials are particularly vital in the subgroups of babies with hypoxic-ischaemic encephalopathy and preterm brain injury in order to establish whether or not treatment to electrical quiescence can improve neurodevelopmental outcome. In our view, an objective measure of the seizure burden with EEG would serve to define success (a reduction of the seizure burden by 80% or more) and would avoid the common problem of over-treating babies who have subtle abnormal clinical signs with multiple AEDs, leading to a prolonged intensive care course and confounding of clinical signs. AEDs suitable for evaluation include topiramate, levetiracetam and perhaps even bumetanide. Babies with seizures are a high-risk group who have been neglected for far too long, receiving a standard of investigation and treatment that is now lagging way behind that offered to older children and adults; for their sakes we urge change.

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