

eNeonatal Review

Jointly Presented by The Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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Concomitant with the increasing use of continuous (a)EEG monitoring in the neonatal intensive care is the awareness that subclinical seizures are very common in neonates with clinical seizures, raising questions about the effectiveness of anti-epileptic drugs in neonates. These drugs were originally tested and used in adults and older children; however, the immature brain reacts differently to anti-epileptic drugs compared to adult brains, and the seizure types can be very diverse even within a patient. Further, both long-lasting seizures as well as anti-epileptic drugs may have adverse effects on the developing brain.

In this issue, we review recent research that raises our clinical awareness of the dilemmas in these areas, including the choice of anticonvulsant agents, the incidence of epilepsy, and automated seizure detection.

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This Issue

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- **ASK THE AUTHOR**

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Mona C. Toet, MD
Faculty Disclosure: No relationship with commercial supporters.

Linda de Vries, MD
Faculty Disclosure: No relationship with commercial supporters.

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Learning Objectives

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At the conclusion of this activity, participants should be able to:

- Discuss why continuous monitoring in the NICU is essential
- Recognize that fifty to sixty percent of the neonatal seizures are 'subclinical' (seizure discharges without clinical manifestations)
- Summarize why neonatal seizures are difficult to treat

Commentary

The incidence of neonatal seizures is 3.5/1000 live births¹, with hypoxic-ischemic brain injury the most common cause of seizures in the neonatal period. Clinical manifestations of neonatal convulsions are very diverse and not always easy to recognize, especially when they are subtle. Continuous EEG monitoring often reveals electrographic seizures (discharges without clinical manifestations), especially following initiation of therapy for clinical seizures^{2,3}. Only with the use of continuous monitoring can subclinical seizures be detected. So far there is no agreement as to whether these subclinical seizure discharges should be treated, although some studies suggest an adverse effect on neurodevelopmental outcome^{4,5}. Recent findings in animal studies show that neonatal seizures adversely affect the developing brain, as do anti-epileptic drugs⁶⁻¹⁰.

Three recent publications^{2,3,11} show that anticonvulsants, effective in adults, are not as effective in neonates. On the other hand, the neonatal brain appears uniquely susceptible to seizures because neonatal gamma-aminobutyric acid (GABA) receptors are excitatory (instead of inhibitory as in adults), and are functionally more active at this stage of life than are *N*-methyl-D-aspartate receptors. In this context, the hypothesis that a diuretic drug such as bumetanide could be used as an anti-epileptic drug in neonates is of particular interest^{12,13}. The severity of the seizures appears to be a stronger predictor of the success of treatment than the assigned agent¹¹, a hypothesis confirmed by Boylan et al², who report that electrographic seizures were common in infants who had severe hypoxic ischemic encephalopathy, particularly after treatment with phenobarbital.

Considering the potential harmful effect of anti-epileptic drugs as described by Bittigau et al¹⁰, should the clinician give a maintenance dose of anti-epileptic drugs after the initial treatment of neonatal seizures to prevent post-neonatal seizures? The question is further complicated by the report by Toet et al¹⁴, showing

that post-neonatal epilepsy occurred in only 9.4 % of the patients following treatment of clinical and subclinical neonatal seizures. Following perinatal arterial stroke, the incidence of post-neonatal epilepsy was higher (18%), suggesting that that treatment of subclinical seizures may be of additional value. With the "real EEG" readings now available on the new digital aEEG machines, seizures have become easier to differentiate from artifacts, allowing for potential interventions.

The large variety of characteristics of the neonatal seizure make automatic seizure detection methods very difficult to implement, as was recently shown by Faul et al¹⁵. The authors report that neonatal seizures tend to migrate throughout the brain, contain rhythmic activity that can vary in frequency, and that multifocal seizures are common in neonates and often display simultaneous independent focal electrographic signatures. The morphology of the electrographic neonatal seizures also varies tremendously between individuals, and can vary within the seizure. Further, neonatal seizures often evolve in amplitude, but may suddenly end when reaching a maximum, or may continue and gradually wane.

There remain many questions to be answered about how to treat neonatal seizures most effectively. While continuous (a)EEG monitoring is an essential tool in providing answers, thoroughly effective and reliable automated neonatal seizure detection remains a long way in the future.

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12. Dzhala V.I, Talos D.M, Sdrulla D.A, Brumback A.C, Mathews G.R, Benke T.A, Delpire E, Jensen F.E, Staley K.J. [NKCC1 transporter facilitates seizures in the developing brain](#). Nature Medicin 2005; 11: 1205-1213.
13. Fukuda A. [Diuretics soothes seizures in the newborns](#). Nature Medicin 2005; 11: 1153-1154.
14. Toet MC, Groenendaal F, Osredkar D, van Huffelen AC, de Vries LS. [Post neonatal seizures following aEEG detected neonatal seizures](#). Pediatr Neurol 2005; 32: 241-247.
15. Faul S, Boylan G, Connonly S, Marnane L, Lightbody G. [An evaluation of automated neonatal seizure detection methods](#). Clinical Neurophysiology 2005; 116: 1533-1541.

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Dzhala V.I, Talos D.M, Sdrulla D.A, Brumback A.C, Mathews G.R, Benke T.A, Delpire E, Jensen F.E, Staley K.J. **NKCC1 transporter facilitates seizures in the developing brain**. Nature Medicine 2005; 11: 1205-1213. With a commentary of Dr Fukuda on this paper:

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Fukuda A. **Diuretics soothes seizures in the newborns**. Nature Medicine 2005; 11: 1153-1154.

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Conventional anticonvulsant drugs often target the gamma-aminobutyric acid (GABA_A) chloride channel, which operates differently in adult and infant brains. Immature neurons contain high levels of chloride ions and express high levels of NKCC1, a co-transporter that uses the electrochemical gradient of both sodium and potassium to cause the accumulation of chloride in neurons. Dzhala et al tested the hypothesis that inhibition of NKCC1 activity with a drug that targets a chloride transporter particularly active in children would reduce the concentration of intracellular chloride in immature cortical neurons, which in turn would reduce GABA_A receptor-mediated excitation, or convert the GABA response to inhibitory and thus provide anticonvulsant effect.

The investigators found that NKCC1 was highly expressed in both neonatal rat and human cortex and that bumetanide, a diuretic drug, inhibited cortical seizure activity in neonatal rats both in vitro and in vivo at doses that have already been extensively tested/used in human neonates.

PHENOBARBITAL AND PHENYTOIN NOT VERY EFFECTIVE IN NEONATAL SEIZURES

Painter M.J, Sher M.S, Stein A.D, Armatti S, Wang Z, gardiner J.C, Paneth N, Minnigh B, Alvin J. **Phenobarbital compared with Phenytoin for the treatment of neonatal seizures**. N Eng J Med 1999; 341: 485-489.

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Painter et al describe a single-blinded study for treatment of neonatal seizures, wherein 59 infants (term and preterm) were randomly assigned to treatment with phenobarbital or phenytoin. Neonates whose seizures were not controlled by the assigned drug were then treated with both drugs. All neonates had continuous EEG recordings for 24 hours, starting from the time of the EEG that determined their eligibility for the trial, or until both drugs had proved to be ineffective. Seizures control was assessed by EEG criteria.

The investigators found that seizures were controlled in 13 of the 30 neonates assigned to receive phenobarbital (43%) and 13 of the 29 neonates assigned to receive phenytoin (45%). When combined treatment was considered, seizure control was achieved in 17 (57 %) of the neonates assigned to receive phenobarbital first and in 18 (62%) of those assigned to receive phenytoin first (p=0.67). The authors further note that severity of the seizures was a stronger predictor of the success of treatment than the assigned agent.

In summation, the authors found that phenobarbital and phenytoin are both equally ineffective in complete seizure control in neonates.

THE INCIDENCE OF POST-NEONATAL EPILEPSY AFTER NEONATAL SEIZURES IS LOW

Toet MC, Groenendaal F, Osredkar D, van Huffelen AC, de Vries LS. **Post neonatal seizures following aEEG detected neonatal seizures**. Pediatr Neurol 2005; 32: 241-247.

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Toet et al addressed the incidence of post-neonatal epilepsy in full-term infants treated with anti-epileptic drugs for neonatal seizure discharges, as detected with amplitude integrated EEG (aEEG). 206 full-term infants were monitored using aEEG, and received anti-epileptic drugs for clinical as well as subclinical neonatal seizures. Follow-up data were analyzed for the development of post neonatal epilepsy, and their neurodevelopmental outcomes assessed at 3, 9, 18 months, 3 and 5 years of age. 169 (82%) neonates received 2 or more anti-epileptic drugs. Overall mortality was 39% (n=80). 41 of the 126 survivors (33%) were abnormal at follow-up, and 12 developed post-neonatal epilepsy (9.4 %).

84 children survived following hypoxic ischemic encephalopathy Sarnat grade II (n=92) and 6 (7%) developed post-neonatal epilepsy. In this subgroup no post-neonatal epilepsy was seen if seizures were controlled within 48 hours after birth and when not more than two anti-epileptic drugs were needed. Twenty-four children survived following intracranial hemorrhage (n=28) and only one (4%) developed post-neonatal epilepsy. Eleven children survived following perinatal arterial stroke (n=13) and 2 (18%) developed post-neonatal epilepsy.

In summation, the authors report that the incidence of post-neonatal epilepsy following treatment of clinical and subclinical neonatal seizures, detected with continuous aEEG, was 9.4%, and was only found in infants with an abnormal neurodevelopmental outcome. This figure is lower than previously reported in children who only received treatment for clinical seizures.

ELECTROGRAPHIC SEIZURES PERSIST AFTER ANTI-EPILEPTIC DRUG USE

Sher M.S, Alvin J, Gaus L, Minnigh B, Painter M. J. **Uncoupling of EEG-clinical neonatal seizures after antiepileptic drug use.** *Pediatr Neurol* 2003; 28:277-280.

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Boylan G.B, Pressler R.M, Rennie J.M, Morton M, Leow P.L, Hughes R, Binnie C.D. **outcome of electroclinical, electrographic, and clinical seizures in the newborn infant.** *Dev Med& Child Neur* 1999; 41: 819-825.

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Sher et al describe a prospective study of the efficacy of seizure cessation by phenobarbital versus phenytoin in 59 term and preterm neonates. They introduced the phenomenon of *uncoupling*: the persistence of electrographic seizures despite the suppression of >50% of the clinical seizures following administration of either one or both anti-epileptic drugs.

The authors found that 58% of the neonates with persistent seizures after treatment had uncoupling of electrical and clinical expression of seizures, with phenobarbital and phenytoin resulting in equal rates of uncoupling. Twenty-four infants responded to the first choice of an anti-epileptic drug with no further seizures.

Boylan et al describe 3 seizure types in 24 neonates (electroclinical, electrographic, and clinical only) using video-EEG for at least 100 minutes within 12 hours of the first seizure. Griffiths neurodevelopmental outcome was assessed in all groups. One of their findings was that electrographic seizures were common in infants who had severe hypoxic ischemic encephalopathy, particularly after phenobarbital treatment.

Both authors found that electrographic neonatal seizures without clinical seizures are very common following anti-epileptic drugs.

AUTOMATED NEONATAL SEIZURE DETECTION: STILL A LONG WAY TO GO

Faul S, Boylan G, Connonly S, Marnane L, Lightbody G. **An evaluation of automated neonatal seizure detection methods.** *Clinical Neurophysiology* 2005; 116: 1533-1541.

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Faul et al evaluated 3 published automated algorithms (Gotman, Liu and Celka) for detecting seizures in neonatal EEG. They tested 43 data files (one-minute, artifact-free EEG segments) containing seizure activity and 34 data files free from seizure activity. In an attempt to obtain improved detection rates, threshold values in each algorithm were manipulated and the actual algorithms were altered. The sensitivity of the 3 algorithms was respectively 62.5, 42.9 and 66.1% with a specificity of 64.0, 90.2 and 56.0%.

The authors conclude that the levels of performance achieved by automated seizure detection algorithms are not high enough for clinical use, reflecting the difficulties involved in detecting seizures in neonates and the lack of a reliable detection scheme for clinical use. The overlap of the frequency characteristics of seizure and non-seizure EEG, artifacts, and natural variances in the neonatal EEG cause great difficulties with the seizure detection algorithms. The algorithm performances figures for this neonatal data set are considerably worse than quoted in the original algorithm source papers.

ADVERSE EFFECTS OF ANTI-EPILEPTIC DRUGS ON THE DEVELOPING BRAIN

Bittigau P, Sifringer M, Genz K, Reith E, Pospischil D, Govindarajalu S, Dzierko M, Pesditschek S, Mai I, Dikranian K, Olney J.W, Ikonomidou C. **Antiepileptic drugs and Apoptosis in the developing brain.** *PNAS* 2002; 99(23): 15089-15094. (*Ann N.Y. Acad. Sci.* 2003; 993: 103-104)

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Wistar rats 0–30 days old received i.p. administration of anti-epileptic drugs, β -estradiol, or normal saline, and were allowed to survive for up to 48 hours after injection. Their brains were analyzed 24 hours later. The investigators looked at histology of the whole brain to visualize degenerating cells and quantify the damage. In addition, total cellular RNA was isolated and total cellular proteins were separated.

In this animal model, the investigators show that at plasma concentrations relevant for seizure control in humans, phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, and valproate all cause apoptotic neurodegeneration. The combination of anti-epileptic drugs with different modes of action appears to result in a substantially higher apoptotic response compared to monotherapy.

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LAST MONTH'S Q & A April 2006 - Volume 3 - Issue 8

Last issue we reviewed the increasing use of continuous (a)EEG monitoring in the NICU, with a particular focus on subclinical seizures, and discussed the effectiveness and risk/reward of anti-epileptic drugs in neonates.



Commentary & Reviews:
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Commentary & Reviews:
Linda de Vries

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We received the following questions from one of our subscribers.

Q As described in the issue, phenobarbitone and phenytoin have been shown to be ineffective in controlling seizures. Which other anti-epileptics are recommended?

A Benzodiazepine drugs such as midazolam and lorazepam are commonly used to control neonatal seizures. However, as there is a sedative effect with these agents that may mask subclinical seizure activity, the clinician should be aware that subclinical seizures may continue in spite of absence of clinical seizures.

Reference:

1. Boylan G.B, Rennie J.M, Chorley G et al. [Second-line anticonvulsant treatment of neonatal seizures](#). Neurology 2004; 62 (3):486-8.

Q Is there a role for lignocaine (lidocaine) in controlling neonatal seizures?

A We and others have also used lignocaine, which, in our experience, appears to be more effective than the benzodiazepines in controlling seizures. However, the drug should only be used in an intensive care setting, as it presents a risk (although a low one) for cardiac arrhythmias. In addition, as both phenytoin and lignocaine have a proarrhythmic effect, it is not recommended to use lignocaine following administration of phenytoin.

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At the conclusion of this activity, participants should be able to:

- Discuss why continuous monitoring in the NICU is essential
- Recognize that fifty to sixty percent of the neonatal seizures are 'subclinical' (seizure discharges without clinical manifestations)
- Summarize why neonatal seizures are difficult to treat

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- Dr. Noguee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.
- Dr. Lehmann has indicated a financial relationship with the Eclipsys Corporation.

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