Controversies in Neonatal Seizure Management

Heung Dong Kim MD, PhD

Department of Pediatrics, Pediatric Epilepsy Clinic
Severance Children’s Hospital
Yonsei University College of Medicine
Significance of Neonatal Seizure

- High incidence
- Indicator of underlying acute encephalopathy
- Different nature from older age
- Prognostic value
- Strong relation to later neurological morbidity
- Limitation of clinical observation: Overdiagnosis and underdiagnosis
Electro-clinical Dissociation

Electroclinical Seizures

Electrographic Seizures

Clinical “Seizures”
Proportion of Subclinical Electrographic Seizures in Neonate

NCS = “no clinical signs”; CS = definite clinical signs

(N = 393 seizures)

(Clancy, Legido & Lewis Epilepsia 1988; 29: 256)
How Do We Detect Neonatal Seizures?

- Clinical (visual) recognition of NS is inherently inaccurate.
- Most electrographic neonatal seizures (ENS) are subclinical.
- There is a strong and growing trend for long term neonatal EEG monitoring.
Causes of Neonatal Seizure

- Reactive seizure by acute encephalopathy: HIE, infarction, hemorrhage, metabolic, trauma, infection, drug intoxication/withdrawal

- Cerebral dysgenesis

- Idiopathic epilepsy in neonate

- Certain genetic disorder

- Neurocutaneous syndrome
Susceptibility of Neonatal Brain to Seizure Activity

- **Extrinsic factors**: risk from birth process
  - Trauma
  - Hypoxic-ischemic encephalopathy
  - Infection

- **Intrinsic factors**
  - High NMDA and AMPA receptor densities
  - Altered composition of NMDA and AMPA receptors to favor excitation
  - Excitatory action of GABA
  - Prolonged action potentials
  - High synaptic density with over-expression of excitatory synapses
  - Delayed development of substantia nigra anticonvulsant networks than proconvulsant networks
  - Delayed maturation of post-synaptic inhibition
Hypoxic-Ischemic Encephalopathy

- Most common cause: 60-65% of neonatal seizures
- Intrauterine asphyxia: meconium staining
- Early neurological depression with gradual recovery
- Seizure onset within 12 hrs. after insult and intensification
- Bilateral brain insult, more damage in watershed area
- EEG: sensitive to underlying brain insult, correlates with severity of hypoxia & later outcome
Strategies to Prevent Ongoing Injury after Hypoxia-Ischemia

- Early identification of high-risk infants
- Supportive care
- Treatment of seizures
- Potential neuroprotective strategies aimed at ameliorating secondary brain injury
  - Hypothermia
  - Oxygen free radical inhibitors and scavengers
  - Excitatory amino acid antagonists
  - Prevention of nitric oxide formation
  - Other neuroprotective measures
Do Neonatal Seizures Cause Brain Damage?

- High incidence of motor deficits, mental handicap, and epilepsy in survivors from neonatal seizure

- Holden et al.: 55 to 70 fold increase of CP, 5.3 fold increase of mental retardation, and 18 fold increase of epilepsy

- More severe prognosis in preterm infants and low birth weight babies: normal outcome in 35% of BWt. less than 2500gm and in 19% of 1500gm or less
Status Epilepticus in Neonatal Seizure

- Cause neuronal damage
- 1/4 to 1/3 of neonatal seizure
- MacBride et al. (2000): group who met at-risk criteria for neonatal seizures, such as hypoxia-ischemia, intraventricular hemorrhage, sepsis, meningitis, and hyponatremia
- Of the 68 selected infants, 40 (58.8%) were having electrographic seizures by EEG monitoring
- Status epilepticus: 43% ranging from 38 minutes to 32 hours
- Thirty percent of infants had refractory not responding to 40 mg/kg of phenobarbital and 20 mg/kg of phenytoin
- Closely related to neurological impairment

- 207 infants enrolled at Baylor or CHOP with video-EEG confirmed seizures
- 28% expired
- 72% survived
- 2 yr follow-up of 86% of the survivors (n=121)
  - abnormal exam 42%
  - MDI<80: 55%
  - PDI<80: 50%
  - epilepsy: 26%

(Mizrahi & Clancy, *Epilepsia* 2001)
Do Neonatal Seizures Cause Harm?


Seizures in the Developing Brain: Perhaps Not So Benign after All

Gregory L. Holmes*† and Yehezkel Ben-Ari‡

*Center for Research in Pediatric Epilepsy
Children's Hospital
Department of Neurology
Harvard Medical School
Boston, Massachusetts 02115

†Laboratoire de Epilepsie et Ischémie Cérébrale
Institut National de la Santé de la Recherche Medicale
Unit 29
75014 Paris
France
Consequences of Neonatal Seizures

- Compared with controls, neonatal rats with recurrent fluothyl induced seizures had, as adults:
  - Impaired spatial learning and memory
  - Decreased activity levels
  - Significantly lower threshold to pentylenetetrazol-induced seizures
  - Sprouting of CA3 mossy fibers

(Holmes et. al. Ann Neurol. 1998)
In the presence of hypoxia, the brain usually switches to an energy saving mode ("off") by blocking synaptic activity.

Generation of seizures "breaks the law of neuronal silence".
# Sequeleae of Neonatal Seizures

<table>
<thead>
<tr>
<th>Sequeleae</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuronal injury</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal brain</td>
<td>Animal</td>
<td>Most studies show absence of neuronal injury with prolonged seizures in neonatal animals. Some studies show mild injury but significantly less than what is seen in more mature animals.</td>
</tr>
<tr>
<td>Metabolically compromised brain</td>
<td>Animal</td>
<td>Increased hippocampal neuronal injury when seizures are superimposed on moderate hypoxic-ischemic brain injury</td>
</tr>
<tr>
<td>Learning/cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal</td>
<td></td>
<td>Impaired performance on water maze, impaired auditory location</td>
</tr>
<tr>
<td>Predisposition to seizures in later life</td>
<td>Animal</td>
<td>Reduced seizure thresholds to flurothyl and pentylenetetrazol and increased spontaneous seizures later in life</td>
</tr>
<tr>
<td>Increased brain injury with subsequent seizures</td>
<td>Animal</td>
<td>Increased degree of hippocampal injury with seizures induced by kainic acid or flurothyl later in life, in animals who previously suffered seizures in early life</td>
</tr>
</tbody>
</table>
MRI Evidence of NS Harm in Human Newborns

(Miller et. al.: Neurology 2002; 58:542)
How Are Neonatal Seizures Treated?

- How effective is standard AED treatment of ENS?
- What is the endpoint of the pharmacologic treatment of neonatal seizures?
Antiepileptic Drugs in Neonatal Seizure

- Phenobarbital
- Phenytoin
- Lorazepam
- Diazepam
Efficacy of Standard AED Treatment of ENS

- 59 untreated neonates with EEG confirmed NS
- Randomly assigned to receive either PB or PHT:
  - 13 of 30 (43%) of PB were Sz free
    - 17 of 30 (57%) Sz free after PHT added to PB
  - 13 of 29 (45%) of PHT were Sz free
    - 18 of 29 (62%) Sz free after PB added to PHT
- No placebo-control group

(Painter MJ et. al. NEJM, 1999)
## Efficacy of AED in Neonatal Seizure

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Number (%) of Patients Achieving Control</th>
<th>Meds Previously Failed for Lack of Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>13/50 (43)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>4/14 (29)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>11/22 (50)</td>
<td>None</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>13/29 (45)</td>
<td>None</td>
</tr>
<tr>
<td>Midazolam</td>
<td>4/6 (67)</td>
<td>Phenobarbital ± phenytoin</td>
</tr>
<tr>
<td></td>
<td>0/3 (0)</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0/3 (0)</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>38/46 (83)</td>
<td>Phenobarbital ± diazepam</td>
</tr>
<tr>
<td></td>
<td>11/13 (85)</td>
<td>Phenobarbital ± diazepam</td>
</tr>
<tr>
<td></td>
<td>3/5 (60)</td>
<td>Phenobarbital</td>
</tr>
</tbody>
</table>
Other AEDs

- Valproate
- Lidocaine
- Topiramate/NBQX
- Zonisamide
- Felbamate
- Levetiracetam
- Lamotrigine
Second-line anticonvulsant treatment of neonatal seizures

A video-EEG monitoring study

G.B. Boylan, PhD; J.M. Rennie, MD; G. Chorley, R.M. Pressler, MD; G.F. Fox, MB; K. Farrer, MB; M. Morton, MB; and C.D. Binnie, MD

Abstract—The authors conducted a randomized trial of second-line anticonvulsant treatments for neonates. The response to treatment was assessed using continuous video-EEG because the clinical diagnosis of seizure in neonates is known to be unreliable. Of 27 neonates with EEG-confirmed seizures, 5 were excluded because of protocol violations, and 11 responded to phenobarbitone in a dose of 40 mg/kg as first line. Three of five neonates treated with lignocaine responded. Six neonates were treated with benzodiazepines as second line: None responded, and their neurodevelopmental outcome was poor.

NEUROLOGY 2004;62:486–488
Second-line AEDs after Phenobarbital

- Neonates with seizures
  - Clinical only seizures
    - Babies treated with phenobarbitone during EEG
      - Responded to Phenobarbitone alone
        - Responder
          - Clonazepam: 0
          - Lignocaine: 3
          - Midazolam: 0
      - Required 2nd line treatment
        - Protocol violations
          - Exit

- EEG seizures
  - Exit
Flupirtine, Selective Opener of KCNQ Channel

A KCNQ Channel Opener for Experimental Neonatal Seizures and Status Epilepticus

Yogendra Sinh H. Raol, PhD,1 David A. Lapides, BA,2 Jeffery G. Keating, PhD,2 Amy R. Brooks-Kayal, MD,1–3 and Edward C. Cooper, MD, PhD4

Objective: Neonatal seizures occur frequently, are often refractory to anticonvulsants, and are associated with considerable morbidity and mortality. Genetic and electrophysiological evidence indicates that KCNQ voltage-gated potassium channels are critical regulators of neonatal brain excitability. This study tests the hypothesis that selective openers of KCNQ channels may be effective for treatment of neonatal seizures.

Methods: We induced seizures in postnatal day 10 rats with either kainic acid or flurothyl. We measured seizure activity using quantified behavioral rating and electrocorticography. We compared the efficacy of flupirtine, a selective KCNQ channel opener, with phenobarbital and diazepam, two drugs in current use for neonatal seizures.

Results: Unlike phenobarbital or diazepam, flupirtine prevented animals from experiencing development of status epilepticus when administered before kainate. In the flurothyl model, phenobarbital and diazepam increased latency to seizure onset, but flupirtine completely prevented seizures throughout the experiment. Flupirtine was also effective in arresting electrographic and behavioral seizures when administered after animals had developed continuous kainate-induced status epilepticus. Flupirtine caused dose-related sedation and suppressed electroencephalographic activity but did not result in respiratory suppression or result in any mortality.

Interpretation: Flupirtine appears more effective than either of two commonly used antiepileptic drugs, phenobarbital and diazepam, in preventing and suppressing seizures in both the kainic acid and flurothyl models of symptomatic neonatal seizures. KCNQ channel openers merit further study as potential treatments for seizures in infants and children.

Kainate–induced increases in electroencephalographic (EEG) power parallel clinical seizure activity and are reversed by flupirtine, phenobarbital, or diazepam. (A) Control, (B) flupirtine (FLUP), (C) phenobarbital (PHB), and (D) diazepam (DIAZ). EEG data were analyzed for total power and power at various frequencies (see Materials and Methods). For each experimental condition, the top panel shows total EEG power within 1–minute intervals before and after the administration of kainic acid and the indicated therapeutic drug (or vehicle). Time points where EEG artifacts because of handling for injection are shown (red–filled circles). The bottom panels show power per minute within 1Hz frequency bins, calculated by Fourier transformation of the EEG and displayed in color according to the scale bar (inset in A). For each experimental condition, kainic acid (KA) treatment results in progressive increase in total power; in spectral plots, this is first detected at lower frequencies and later at higher frequencies. Note the rapid onset and sustained reduction in power after flupirtine administration. Phenobarbital shows a persistent band (light blue) of increased power at 15 to 30Hz. Diazepam is effective at power suppression in the first 20 minutes of treatment, but power increases prominently at later time points.
Endpoint of AED’s

- Clinical recognition and quantification are difficult and unreliable
- AEDs frequently uncouple clinical and electrographic seizures
- Complete elimination of all the electrographic neonatal seizures determined by EEG monitoring
Neonatal seizures are one of the most common neurological disorders in infants. However, the optimal treatment strategy for neonatal seizures remains controversial and there is little data regarding current treatment of neonatal seizures. In this study we describe the current treatment of neonatal seizures and variation in practice among 31 pediatric hospitals in the United States. We retrospectively identified 6099 infants hospitalized in the first month of life in one of 31 pediatric hospitals participating in the Pediatric Health Information System, with a discharge diagnosis of seizure. As expected, most treated infants received phenobarbital.

However, there was significant interhospital variability for all treatments studied including any antiepileptic drug treatment, phenytoin treatment, antiepileptic drug treatment through discharge, number of antiepileptic drugs used, and treatment with pyridoxine ($P < .001$). These findings highlight the need for rigorous controlled outcome studies to determine optimal therapy for neonatal seizures and devise treatment standards.

Keywords: neonatal seizure; antiepileptic drugs; seizure treatment; phenobarbital
### AEDs Treatment of Neonatal Seizures

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Total Infants, N = 6099, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any NBAED</td>
<td>4746 (77.8)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>4618 (75.7)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>981 (16.1)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>99 (1.6)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>28 (0.5)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>28 (0.5)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>22 (0.4)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>20 (0.3)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>4 (0.07)</td>
</tr>
<tr>
<td>Felbamate</td>
<td>4 (0.07)</td>
</tr>
<tr>
<td>Any NBAED other than phenobarbital or DPH</td>
<td>190 (3.1)</td>
</tr>
<tr>
<td>Any Benzodiazepine</td>
<td>3136 (51.4)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2312 (37.9)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1567 (25.7)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>163 (2.7)</td>
</tr>
</tbody>
</table>

Note: NBAED, nonbenzodiazepine antiepileptic drug.
Inter-hospital Variability of AEDs Maintenance until Discharge

Mean: 67%
Maintenance of AED’s

- Variable duration in practice
- Discontinue AED’s before discharge to 2 years
- Depend on cause, severity, recovery, neurological outcome, EEG abnormality
- Usually reevaluation in 1-2 months after discharge to discontinue
Epilepsy with Onset in Neonate

- Idiopathic neonatal epilepsy
  - Benign familial neonatal convulsion
  - Benign (idiopathic) neonatal convulsion
- Epilepsy from MCD
- Early infantile epileptic encephalopathy
- Early myoclonic epilepsy
Case of Ohtahara Syndrome

- Onset: 10 day
- Ictus
  ① spasms at 10 days
  ② 5 mo. of age: vacant staring (or EBD) with smiling (or drooling) --> sometimes Rt. extrimities tonic sz
- Frequency: 20~30/day, 2~3 day/wk
- Duration: 5~20 sec
Case of Ohtahara Syndrome: EEG
Case of Ohtahara Syndrome: ictal EEG and Post-op MRI
Metabolic disturbances

- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Aminoacidopathies
- Urea cycle disorders
- Pyridoxine dependency
- Biotinidase deficiency
- Glucose transporter deficiency
- Mitochondrial disorders
- Defects in betaoxidation
- Peroxisomal disorders
## Treatable Metabolic disturbances

**Table 1** Examples of treatable neonatal metabolic epilepsies

- Pyridoxine dependency
- Pyridoxal phosphate dependency
- Folinic acid responsive seizures
- Serine deficiency
- Glucose transporter 1 deficiency
- Biotinidase deficiency
- Creatine deficiency
- Untreated Phenylketonuria
Pyridoxine dependency

- birth incidence between 1:400 000 and 1:750 000 (Baxter 2003)
- Characterized by multiple seizure types refractory to standard antiepileptic therapy, progressive encephalopathy and ultimately death if treatment is not initiated
- Diagnosis is usually established via a therapeutic trial of intravenous pyridoxine 100 mg during EEG monitoring
- Alternative approaches have been described, including intravenous doses as high as 500 mg to effect a response, or daily enteral doses of 15 mg/kg of pyridoxine with one week of observation
Pyridoxine dependency

- No clear consensus or evidence for the optimal dosage of pyridoxine for lifelong maintenance
- Improvement in IQ of 1 SD across both verbal and performance subscales after the pyridoxine dose was increased from 50 to 150 mg/day (0.8 to 2.6 mg/kg per day)
- Dosage may be limited by the adverse effects of a painful sensory neuropathy, rash, or photosensitivity. A dosage of 50 mg/kg per day of pyridoxine has been recommended for patients who weigh 30 kg or less
- Maximal maintenance dose of 500 mg is sometimes recommended
B₆ Metabolism to Active Form of Pyridoxal 5’-Phosphate

Pearl PL, J Inherit Metab Dis (2009) 32:204–213
## Function of Pyridoxal 5’-Phosphate Dependent Enzymes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic amino-acid decarboxylase</td>
<td>Dopamine, serotonin synthesis</td>
</tr>
<tr>
<td>2-oxoglutarate aminotransferase</td>
<td>Glutamate synthesis</td>
</tr>
<tr>
<td>GABA transaminases</td>
<td>GABA catabolism</td>
</tr>
<tr>
<td>Glutamic acid decarboxylase</td>
<td>GABA synthesis</td>
</tr>
<tr>
<td>Glycine cleavage system</td>
<td>Glycine catabolism</td>
</tr>
<tr>
<td>Kynureninase</td>
<td>Quinolinic acid synthesis</td>
</tr>
<tr>
<td>Kynurenine aminotransferase</td>
<td>Kynurenic acid synthesis</td>
</tr>
<tr>
<td>L-Serine racemase</td>
<td>D-serine synthesis</td>
</tr>
</tbody>
</table>
Pyridoxal phosphate (PLP) dependency

- Pyridoxal 5-phosphate (PLP): biologically active form of pyridoxine
- PLP is a co-factor for approximately 100 enzymatic reactions, many of which are vital for the synthesis, function, and catabolism of neurotransmitters
- Considerable range of clinical phenomenology;
  - Seizure semiology included myoclonias, eye deviation, facial grimacing, flushing, and diaphoresis
  - EEG abnormalities ranged from a burst-suppression pattern to isolated focal spike discharges
- CSF evaluation disclosed inconsistent increases in serine, threonine, and glycine concentrations
- Consistent response to PLP at 50–100 mg/kg/d in six divided doses
Folinic acid-responsive seizures

- Seizures respond promptly to 2.5–5 mg given twice daily of folinic acid (leucovorin), with doses up to 8 mg/kg per day
- Role of folinic acid remain unexplained
- Folinic acid is generally added for patients with an incomplete response to pyridoxine or PLP treatment, although further studies are needed to establish the optimal treatment regimen
Serine synthesis disorders

- Defects in the synthesis of L-serine lead to a syndrome of congenital microcephaly, neurodevelopmental disability, and epilepsy which may have neonatal onset.
- Plasma amino acid analysis will demonstrate decreased concentrations of serine and often glycine.
- L-serine at a dosage of 500 mg/kg per day and glycine 200 mg/kg per day and prenatal and postnatal supplementation have been effective.
Glucose transporter I deficiency

- Deficient glucose transport across the blood–brain barrier
- CSF examination reveals decreased glucose level
- Clinical phenotype: ranging from neonatal seizures to infantile myoclonic epilepsies, early childhood absence seizures, non-specific developmental disorders, or acquired ataxia
- Ketogenic diet is treatment of choice to provide an alternative brain fuel
Case (male, 4 mo of age)

Ictus: cyanosis, apnea
Onset: 생후 5일
Medication:
- Carbamazeipine 260mg #2
- Sentil 2mg #2
- Phenobarbital 40mg #2
- Orfil 3cc #2
- Pyridoxine 50mg #2
CSF glucose 22/Serum glucose 106
CSF amino acid: Alanine 33.7(nmol/ml)
KD ratio at 2: 1 with 100kcal/kg from HOD #4
Case (male, 4 mo of age)
DEND: Developmental delay, epilepsy, neonatal diabetes

- Severe neonatal onset epileptic encephalopathy and DM
- Treatable channelopathy involving potassium channel (KATP)
- This channel normally closes when the ATP/ADP ratio rises with increased blood glucose, and the cell depolarizes, which leads to physiological insulin release in response to blood glucose
- Insulin is not effective
- Sulfonylurea, an oral hypoglycaemic agent, binds to the channel, promoting closure and physiological insulin release
- Prompt recognition and treatment with oral hypoglycaemic agents and not systemic insulin administration is essential for a good neurological outcome
Approaches to Neonatal Seizures of Unidentified Etiologies

- Rule out typical aetiologies (infection, hypoglycaemia, hypocalcaemia, etc.) plus plasma amino acids (special attention to serine and glycine)
- Urine for α-amino adipic semialdehyde, pipecolic acid
- CSF for glucose, pyridoxal phosphate, and biogenic amines
- Emergency EEG with IV pyridoxine 100 mg
- PLP 10 mg/kg/dose × 2 (2 hours apart)
- Folinic acid 5 mg × 2 (6 hours apart)
Summary

- Innocent paroxysmal activity vs. neonatal seizure
- Determine etiology
- High frequency of subclinical seizure
- EEG diagnosis is essential
- Goal of treatment
- Neurological follow-up for sequelae
Thank you for your Attention!!!