Neonatal Seizures

Child Neurology Conference

Dr. Hemang Shah

Terminologies

- Seizure a symptom not a disease
- A stereotypic, paroxysmal spell of altered neurologic function (behavior, motor, and/or autonomic function)
- “Neonatal epilepsy” = “neonatal seizures” ?
- “Neonatal”:

- Term infant: first 28 days of life
- Premature infants: this term usually is applied until gestational age 44 weeks.

Epidemiology

- Incidence of neonatal seizures in term vs preterm infants
  - 1.5-3.0 per 1000 live term births
  - 50-150 per 1000 live preterm births

- Incidence as a function of birth weight
  - 57.5 per l000 in infants < 1500 grams
  - 2.8 per 1000 in infants 2500 to 3999 grams

A population-based study of neonatal seizures in Fayette County, Kentucky {Neurology 1995, retrospective chart review - We ascertained potential cases by computer search of hospital-based medical record systems, Kentucky Center for Health Statistics birth certificate data files, and National Center for Health Statistics multiple-cause-of-death mortality data files}

The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. AU Ronen GM; Penney S; Andrews W SO J Pediatr 1999 Jan;134(1):71-5.

Incidence of neonatal seizures in Harris County, Texas, 1992-1994. AU Saliba RM; Annegers JF; Waller DK; Tyson JE; Mizrahi EM SO Am J Epidemiol 1999 Oct 1;150(7):763-9.

Semiology // Clinical aspects

- Do we actually know how neonatal seizure look like?
- Show videos

Why do seizures manifest differently in neonates?

- Seizure in newborns differ from those seen in older children and adults
- Seizures in preterm infants differ from term infants
  - Newborns rarely have well organized, generalized tonic-clonic seizures
  - Preterm infants have even less well organized spells than term infants

Immature brain seems more prone to seizures than the more mature brain

↓

Differences relate to the status of neuroanatomical and neurophysiological development in the perinatal period

Why do seizures manifest differently in neonates?

- Perinatal anatomical features
  - Neurite growth (dendritic and axonal ramifications) are still in process
  - Synaptogenesis is not complete
  - Deficient myelination in cortical efferent systems
    - Prevents conduction of epileptic discharges throughout the brain in a generalized fashion

Result in weakly propagated , fragmentary, focal and short lasting seizures which may not be apparent on EEG

Newborn monkey have more advanced cerebral cortical organization, myelination of cortical efferent systems and interhemispheric commisures

↓

Generalized seizures apparent clinically and electrographically

Why do seizures manifest differently in neonates?

- Perinatal anatomical features
  - Limbic system with connections to midbrain and brainstem is more developed than the cerebral cortical organization
    - Higher frequency of oral-buccal-lingual clinical manifestations of neonatal seizures
      - Sucking, chewing, drooling, oculomotor phenomena (eye deviation) and apnea

Why do seizures manifest differently in neonates?

- Neurophysiological features
  - In limbic and neocortical regions
    - excitatory synapses develop before inhibitory synapses
    - in early development, GABA acts to produce excitation rather than inhibition
  - Immature hippocampal and cortical neurons are more susceptible to seizure activity than mature neurons

Why do seizures manifest differently in neonates?

- Neurophysiological features
  - Deficient development of substantia nigra system for inhibition
    - only the proconvulsant projection network functions in early brain development
  - Impaired propagation of electrical seizures and synchronous discharges recorded from surface EEG may not correlate with behavioral seizure phenomena
    - Due to deficient myelination of the cerebral efferent systems

Classification of Neonatal Seizures

Clinical Seizure	EEG Correlation		
	Common	Uncommon	*Non epileptic?*
Subtle	+		
Clonic			
Focal	+		
Multifocal	+		
Tonic			
Focal	+		
Generalized		+	*Brain stem release phenomena ?*
Myoclonic			
Focal		+	
Multifocal		+	
Generalized	+		

Quiz: Which brainstem structure stimulation causes seizure?

Subtle Seizures

- Selected Major Manifestations

  - Ocular phenomena
    - Tonic horizontal deviation of eyes with or without jerking of eyes (term)
    - Sustained eye opening with ocular fixation (pre-term)
  - Oral-buccal-lingual movements
    - Chewing, sucking, lip smacking (pre-term)
  - Limb movements
    - Cycling, swimming, rowing
  - Autonomic phenomena
    - Increase in blood pressure, brady/tachycardia
  - Apneic spells (term) (lesslikely to be associated with bradycardia)

// more common in preterm neonates //

Clonic Seizures

- Usually involve one limb or one side of the body jerking rhythmically at 1-4 times per second
- Focal Clonic Seizures
  - Well localized clonic jerking
  - Infant usually not unconscious
- Multifocal Clonic Seizures
  - Involves several parts of the body in migrating fashion (nonordered fashion – nonjacksonian migration ;)
  - Simultaneous or in sequence

Tonic Seizures

- Focal Tonic Seizures
  - Sustained posturing of limb
  - Asymmetrical posturing of trunk and neck
- Generalized Tonic Seizures (common) {startle disease/congenital stiff-man syndrome}
  - Tonic extension of upper and lower limbs (mimics decerebrate posturing)
  - Tonic flexion of upper limbs and extension of lower limbs (mimics decorticate posturing)
  - Most are not accompanied by EEG seizure discharges (only 15-30% have EEG correlates)

Myoclonic Seizures

- Usually faster than clonic activity, predilection for flexor muscles, not associated with EEG discharges.

- Focal
  - Typically involve flexor muscle of upper extremity
- Multifocal
  - Asynchronous twitching of several parts of the body
    Generalized Myoclonic Seizure

- Generalized Myoclonic Seizure
  - Single or several bilateral synchronous jerks of flexion, occur more in upper than lower limbs (d/d infantile spasm?)

What normal neonatal activity is mistaken for seizure?

- Benign paroxysmal neonatal motor phenomena
- Awake or drowsy
  - Roving sometimes disconjugate eye movement
  - Sucking or puckering movement not associated with ocular fixation or deviation
- Sleep
  - Fragmentary myoclonic jerks – may be multiple
  - Isolated, generalized myoclonic jerk as infant wakes from sleep

Jitteriness versus seizure

Clinical Feature	Jitteriness	Seizure
Abnormality of gaze or eye movement	--	+
Movements stimulus sensitive	+	--
Predominant movement	Tremor	Clonic jerking
Movements cease with passive flexion	+	--
Autonomic changes	--	+

Etiology of being jittery: HIE, hypoglycemia, hypocalcemia, drug withdrawal,

What is epileptic and non-epileptic seizure?

Epileptic

- Generated by hypersynchronous discharges that may spread and activate other brain structures
- Cannot be provoked by tactile stimulation
- Cannot be suppressed by restraint of involved limb or repositioning of infant
- Consistently associated with electro-cortical seizure activity on EEG

Non-epileptic

- Paroxysmal clinical phenomena that are not consistently associated with EEG seizure activity
- Provoked by stimulation
- Suppressed by restraint and repositioning of infant

What are the causes of neonatal seizures ?

Cause	Frequency
Hypoxic-ischemic encephalopathy *(Day 1)*	30-53%
Intracranial hemorrhage *(SAH : Day 2 // well baby with seizures)*	7-17%
Cerebral infarction	6-17%
Cerebral malformations (Lissencephaly/pachygyria)	3-17%
Meningitis/septicemia	2-14%
Metabolic	
Hypoglycemia	0.1-1.5%
Hypocalcemia, hypomagnesemia	4-22%
Hypo/Hypernatremia	
Inborn errors of metabolism	3-4%
Pyridoxine deficiency	
Kernicterus	1%
Hyperammonemia	
Maternal drug withdrawal	4%
Idiopathic	2%
Benign idiopathic neonatal seizures	1%
Neonatal epileptic syndromes	
Congenital infections	
Unintentional injection of local anesthetic during labor	
Maternal vitamin D deficiency	

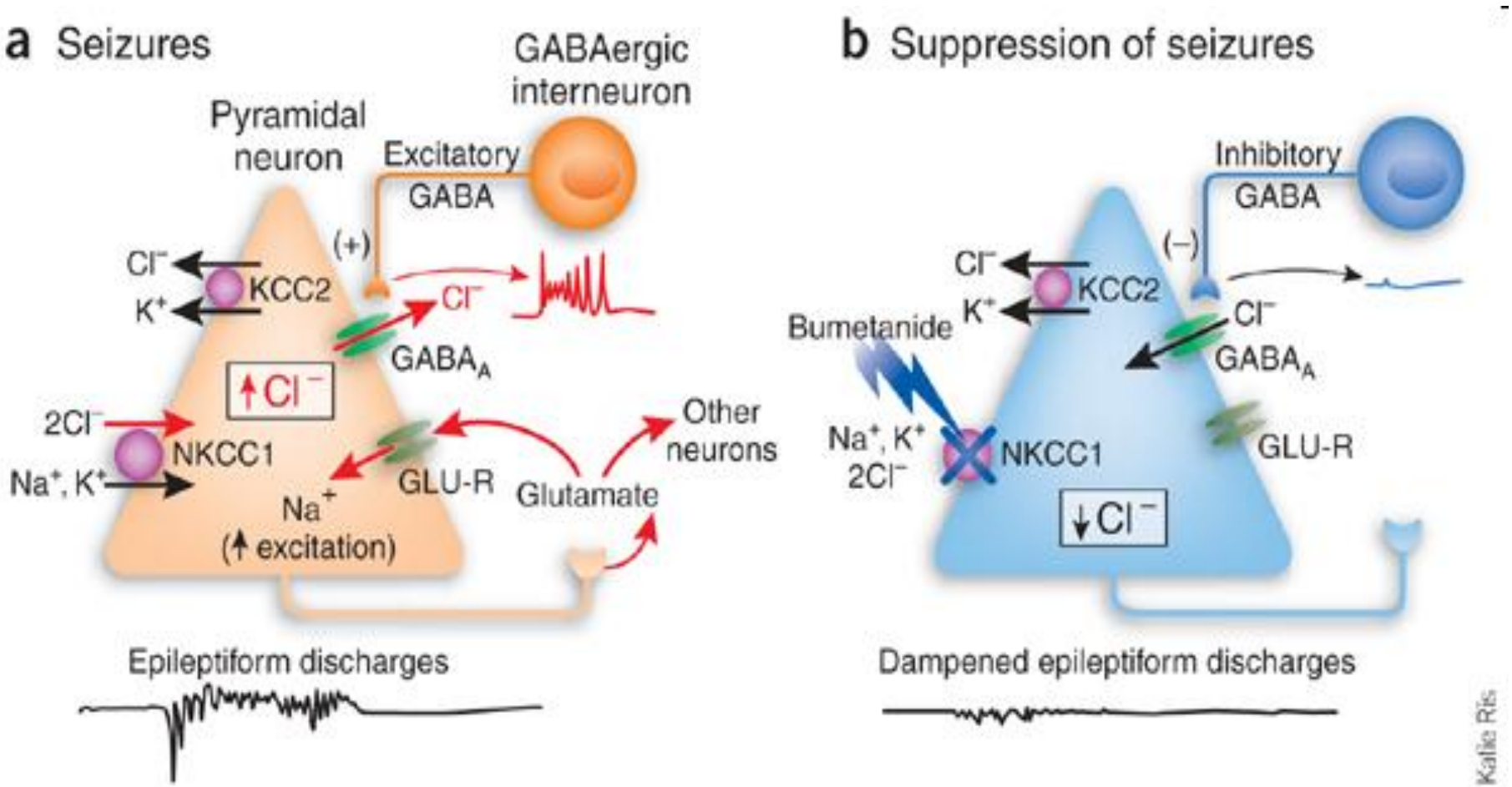
Etiologies in relation to time of onset and relative frequency

Etiology	Time of Onset		Relative Frequency	
	0-3 days	> 3 days	Premature	Full Term
HIE	+		+++	+++
Intracranial Hge	+	+	++	+
Intracranial Infx	+	+	++	++
Developmental Defects	+	+	++	++
Hypoglycemia	+		+	+
Hypocalcemia	+	+	+	+
Other metabolic disturbance	+			+
Epileptic syndromes	+	+		+

* Benign ideopathic neonatal seizure, Benign neonatal sleep myoclonus etc.*

Volpe JJ. Neonatal seizures. In: Neurology of the Newborn; 2008.

Pathogenesis

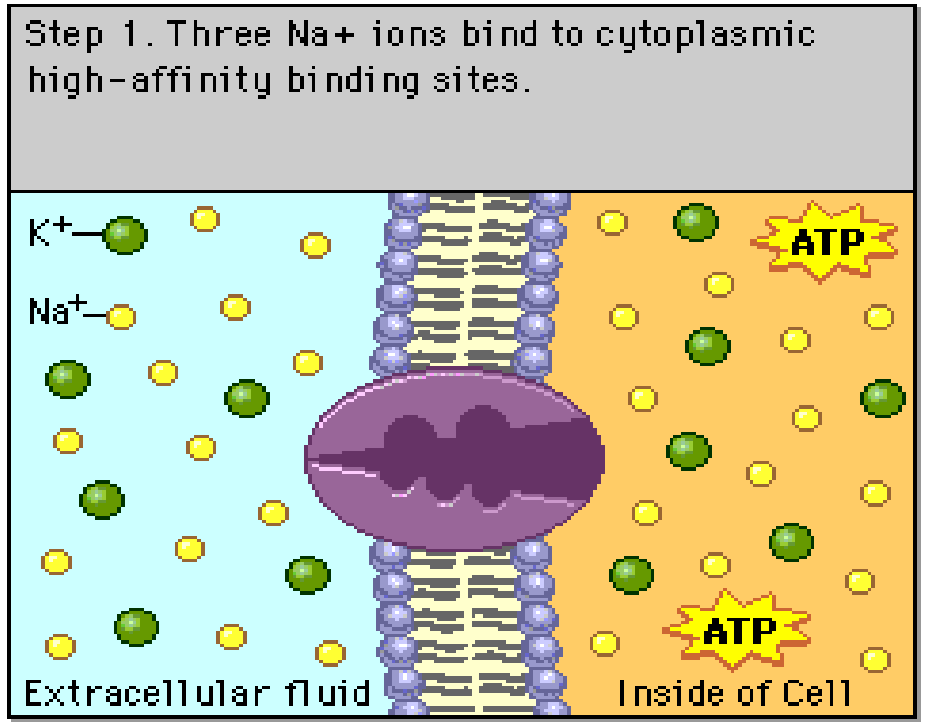


* Pyridoxine Saga *

* Neuroanatomical and Neurophsiological basis *

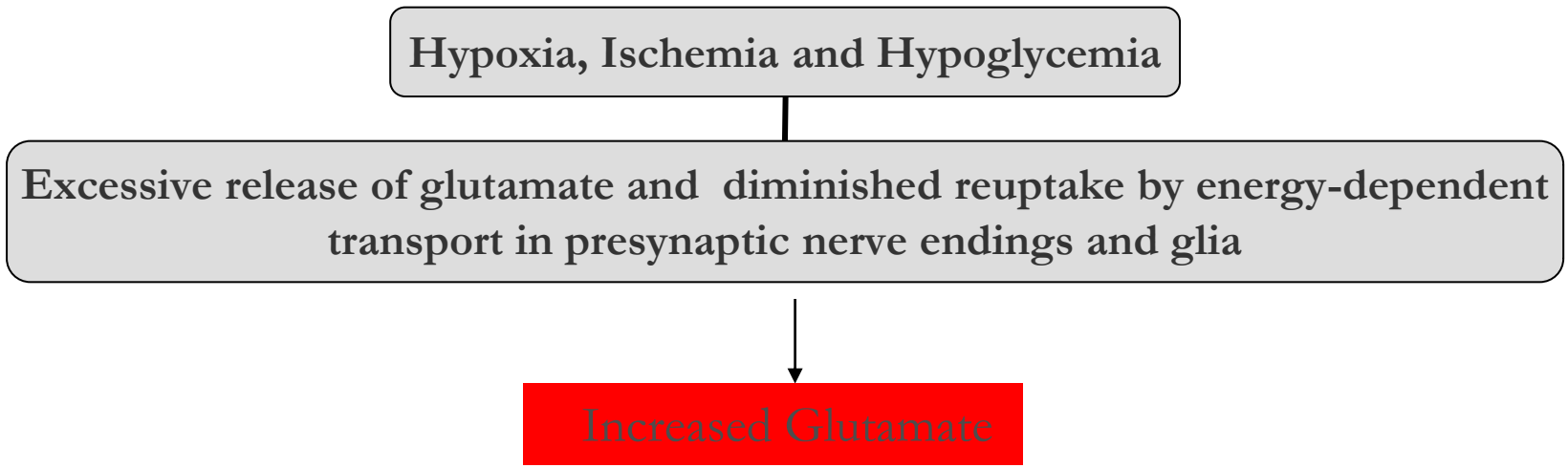
Why is the neonatal brain prone to seizures?

- Seizure results when there is excessive synchronization of electrical discharge or depolarization of neurons within the central nervous system (CNS)
- Depolarization – inward migration of sodium
- Maintenance of membrane potential requires energy (ATP) which extrudes Na and takes in K



Why is the neonatal brain prone to seizures?

- Relative excess of excitatory vs inhibitory neurotransmitter result in excessive depolarization
  - Glutamate is the prinicipal excitatory neurotransmitter in the cortex



Why is the neonatal brain prone to seizures?

- Relative deficiency of inhibitory vs excitatory neurotransmitter result to excessive depolarization
  - GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter

1. "Pyridoxine dependency"

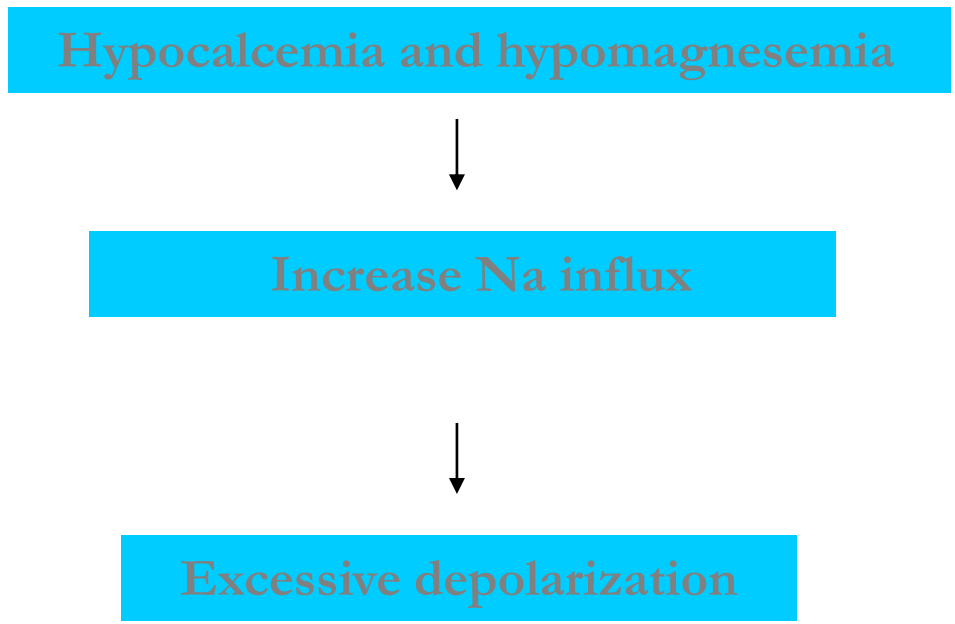
Pyridoxine is a critical cofactor of Glutamic acid decarboxylase (synthetic enzyme of GABA)

Disturbance in binding results to decreased GABA

2. Inhibitory synapses were blocked and not well developed

Why is the neonatal brain prone to seizures?

- Calcium and magnesium interact with the neuronal membrane to cause deviation of Na movement

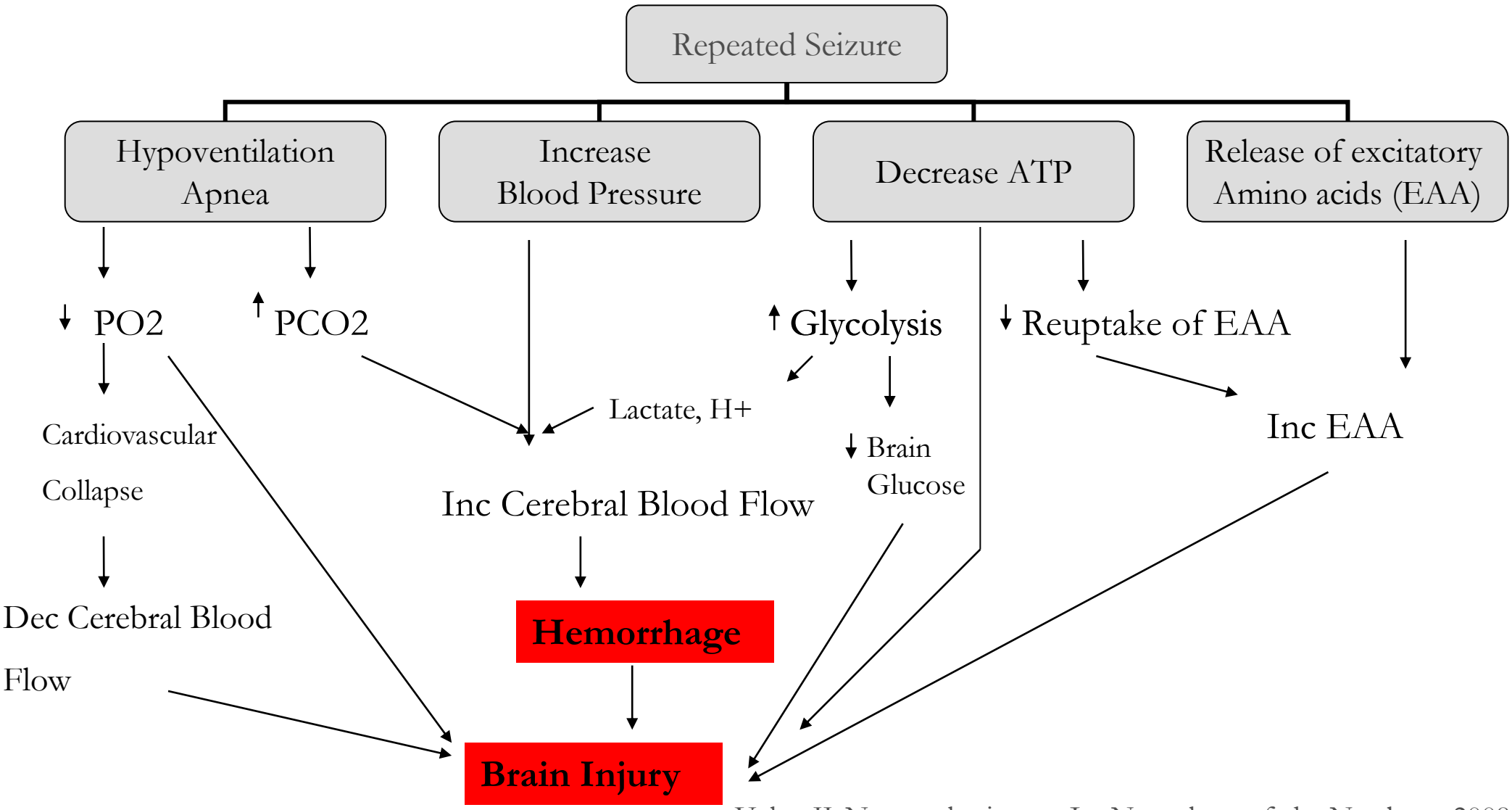


Probable Mechanisms of Some Neonatal Seizures

PROBABLE MECHANISM	DISORDER
Failure of Na + -K + pump secondary to ↓ adenosine triphosphate	Hypoxemia, ischemia, and hypoglycemia
Excess of excitatory neurotransmitter (eg.glutamic acid—excessive excitation)	Hypoxemia, ischemia and hypoglycemia
Deficit of inhibitory neurotransmitter (i.e., relative excess of excitatory neurotransmitter)	Pyridoxine dependency
Membrane alteration— ↑ Na + Permeability	Hypocalcemia and hypomagnesemia

Volpe JJ.Neonatal Seizures:Neurology of the Newborn.4th ed.

Mechanisms of brain injury with repeated seizures



Volpe JJ. Neonatal seizures. In: Neurology of the Newborn 2008

What is the work-up for neonatal seizure?

- History and physical: most important, least paid ☹

- Blood Tests
  - Glucose, calcium, magnesium, sodium, arterial blood gases
  - Lactate and amino acids if inborn error of metabolism is suspected
- CSF Studies
  - Cell count, glucose, protein, bacterial culture
  - Herpes simplex virus (HSV) polymerase chain reaction and culture if HSV encephalitis is suspected
- Neuro-imaging: CT, MRI
- Urine
  - Urinalysis, toxicology screen

What is the work-up for neonatal seizure?

- Congenital Infection screening
  - Serum titers in mother and child (TORCH)
  - Urine culture for cytomegalovirus
- Inborn errors of metabolism screening
  - Plasma amino acids and organic acids
  - Urine organic acids
  - Serum lactate, ammonia
- Electroencephalogram
- Head sonogram, CT scan, Brain MRI

Electroencephalogram

- Essential in diagnosis and management of neonatal seizures
- Usually obtained during interictal period
- Major values of EEG

  1. Determine if an infant with subtle seizure
     is experiencing epileptic seizure
  2. Determine whether a paralyzed infant is experiencing convulsive phenomena
  3. Define interictal backgrounds which are of value in estimating prognosis

- 9 electrode montage
- Electroclinical dissociation (paradoxical response of GABA)
- Serial and continuous EEG, video monitoring – standard of care (single channel amplitude-integrated EEG for continuous monitoring)
- Ictal patterns: short, focal (centro-temporal>occipital>frontal)
- Focal or multifocal spikes or sharp waves or both and focal monorhythmic discharges, distictive from background. Usually are repetitive, localized and followed by some degree of suppression of background voltage activity.

Why should an infant with neonatal seizures be treated?

- Usually related to significant illness requiring therapy
- Potential adverse effects of seizure on circulation and cerebral metabolism
- Interfere with supportive measures (alimentation and assisted respiration)
- Concern that repeated seizure cause brain injury

•Whom to treat?

•Adequacy of treatment (goal: cessation of clinical Vs electrograhic seizure*)

* Clancy and coworkers: approximately 80% of 393 electrical seizures recorded were not accompanied by clinical seizure activity. 88% of the total population of patients had been treated wth one or more anticonvulsant medications.

How do you treat neonatal seizures?

- Ensure adequate ventilation and perfusion
- If with hypoglycemia
  - Glucose 10% 2 ml/kg IV
- If without hypoglycemia
  - Anticonvulsant therapy
- Etiology-Specific (as indicated)
  - Hypocalcemia (calcium gluconate 5% 4 ml/kg IV)
  - Hypomagnesemia (MgSO4 50% 0.2 ml/kg ***IM,*** *WATCH OUT FOR NM BLOCKDE*)
  - Pyridoxine deficiency (pyridoxine 50-100 mg IV, watch out for apnea)
  - Meningitis (Ampicillin/Cefotaxime)

How are anti-epileptics used in the neonate?

AED	Initial Dose	Maintenance Dose	Route
Phenobarbital	20 mg/kg	3-4 mg/kg/day	IV,IM,PO
Phenytoin	20 mg/kg	3-4 mg/kg/day	IV, PO
Fosphenytoin	20 mg/kg PE	3-4 mg/kg/day	IV,IM
Lorazepam	0.05-0.1 mg/kg	Q 8-12 hours	IV
Diazepam	0.25 mg/kg	Q 8-12 hours	IV

Initial drug of choice – Phenobarbital

Don’t combine diazepam with phenobarb

Riviello JJ. Pharmacology review: drug therapy for neonatal seizures: part 1. NeoReviews 2004;5:215-226.

Expected response of neonatal seizures to sequence of therapy

AED	Cessation of Seizure (%)
Phenobarbital 20 mg/kg	40%
Phenobarbital 40 mg/kg	70%
Phenytoin 20 mg/kg	85%
Lorazepam 0.05-0.10 mg/kg	95-100%

Volpe JJ. Neonatal seizures. In: Neurology of the Newborn 2008

Other anti-epileptic drugs

- Intravenous AEDs

High-dose phenobarbital: >30 mg/kg

Pentobarbital: 10 mg/kg, then 1 mg/kg per hour

Thiopental: 10 mg/kg, then 2 to 4 mg/kg per hour

Midazolam: 0.2 mg/kg, then 0.1 to 0.4 mg/kg per hour ***(less sedation and respiratory depression)***

Clonazepam: 0.1 mg/kg

Lidocaine: 2 mg/kg, then 6 mg/kg per hour

Valproic acid: 10 to 25 mg/kg, then 20 mg/kg per day in 3 doses

Paraldehyde: 200 mg/kg, then 16 mg/kg per hour

Chlormethiazole: Initial infusion rate of 0.08 mg/kg per minute

Dexamethasone: 0.6 to 2.8 mg/kg

Pyridoxine (B6): 50 to 100 mg, then 100 mg every 10 minutes (up to 500mg)

Other anti-epileptic drugs

- Oral AEDs

  Primidone: 15 to 25 mg/kg per day in 3 doses

  Clonazepam: 0.1 mg/kg in 2 to 3 doses

  Carbamazepine: 10 mg/kg, then 15 to 20 mg/kg per day in 2 doses
  Oxcarbamazepine: no data on neonates, young infants

  Valproic acid: 10 to 25 mg/kg, then 20 mg/kg per day in 3 doses

  Vigabatrin: 50 mg/kg per day in 2 doses, up to 200 mg/kg per day
  Lamotrigine: 12.5 mg in 2 doses

  Topiramate: 3 mg/kg per day *(not neurotoxic, NO IV FORM ☹)*

  Zonisamide: 2.5 mg/kg per day

  Levetiracetam: 10 mg/kg per day in 2 doses

  Folinic acid: 2.5 mg BID, up to 4 mg/kg per day

Riviello JJ. Pharmacology Review: drug therapy for neonatal seizures: part 2. NeoReviews 2004; 5:262-273.

How long do you treat?

Determinants of treatment duration

- Neonatal neurological examination
- Cause of neonatal seizure
- Electroencephalogram

- Antiepileptic drugs have detrimental effects on the developing brain*

* Neonatal rats showed apoptotic neurodegeneration within 24 hrs after administration of PHB, PHT, Diazepam, Clonazepam, Valproate except topiramate, levetiracetam

Recommended Guideline

Neonatal period:

- If neonatal neurological examination becomes normal discontinue therapy
- If neonatal neurological examination is persistently abnormal, consider etiology and obtain EEG
- In most such cases

  Continue phenobarbital
  Discontinue phenytoin
  Reevaluate in 1 month

Recommended Guideline

After one month

- If neurological examination has become normal, discontinue phenobarbital
- If neurological examination is persistently abnormal, obtain EEG
- If no seizure activity on EEG, discontinue phenobarbital

Other modes of therapy

- Surgical Option
  - neonatal seizure caused by cerebral malformations/developmental defects recalcitrant to medical therapy
  - surgery usually performed later in infancy

Prognosis

- Prognosis improved over the past decades
- Mortality decreased from 40% to 20%
- Incidence of neurological sequelae (25% to 50%)
  - Mental retardation
  - Cerebral palsy
  - Spasticity
  - Hydrocephalus
  - Epilepsy (17-56%)
  - Feeding difficulties
  - Microcephaly

Prognosis

- In relation to neurological exam
  - Normal – associated with good prognosis
  - Abnormal – predicting poor prognosis

  - Early predictors of poor prognosis
    - 5 minute Apgar score of less than 7
    - Need for resuscitation after 5 minutes of age
    - Seizure lasting > 30 minutes

Mellits ED. Neonatal seizures. A multivariate analysis of factors associated with outcome. Pediatrics.

Prognosis

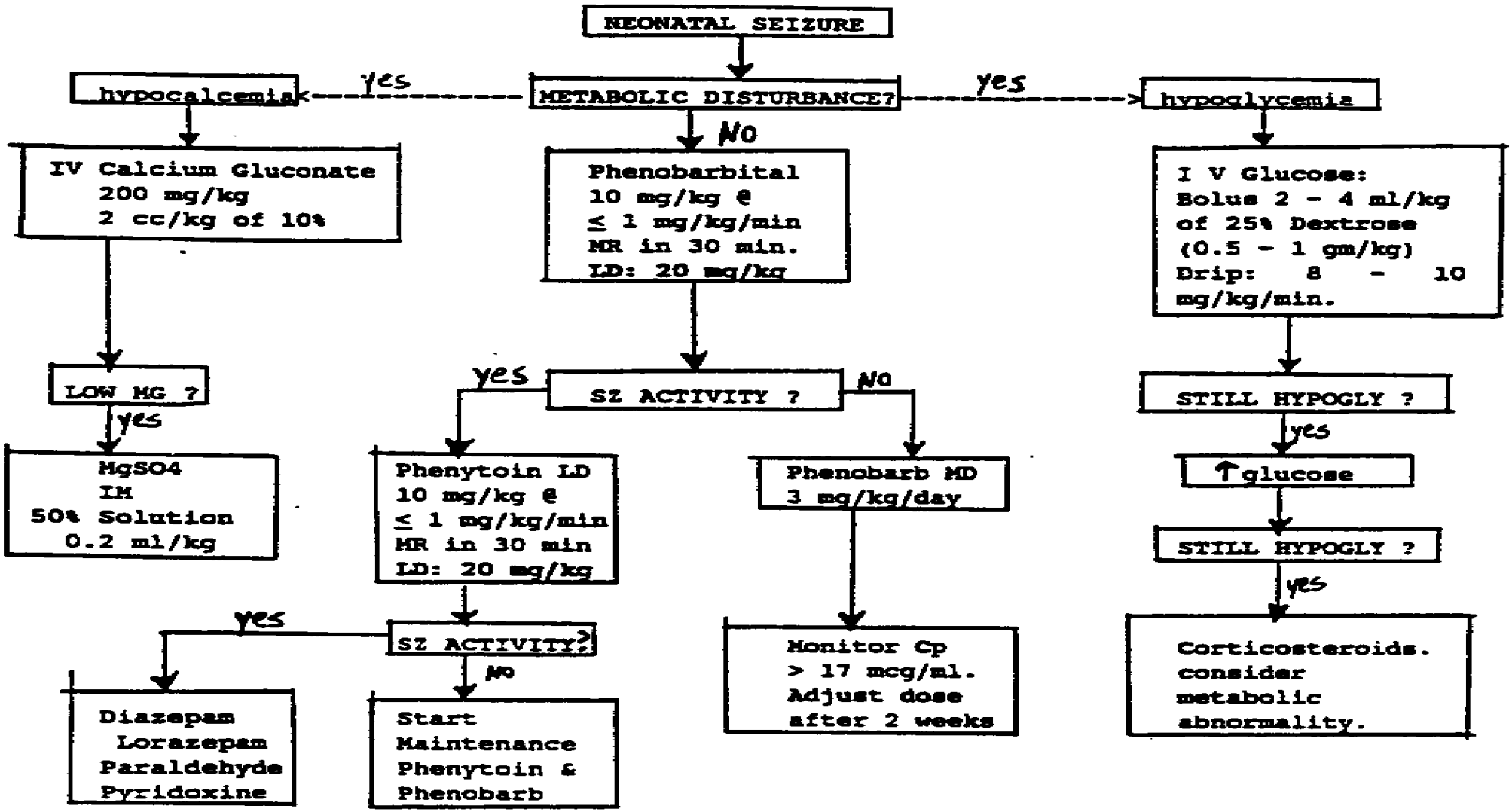
- In relation to EEG
  - If EEG background is normal, the prognosis is excellent for seizures to resolve; normal development is likely
  - Severe EEG background abnormalities indicate poor prognosis; such patients frequently have cerebral palsy and epilepsy
  - The presence of spikes on EEG is associated with a 30% risk of developing future epilepsy

Prognosis

In relation to neurologic disease/etiology

Neurologic Disease	Normal Development (%)
Hypoxic-ischemic encephalopathy	50%
Intraventricular hemorrhage	10%
Primary subarachnoid hemorrhage	90%
Hypocalcemia	
Early onset	50%
Later onset	100%
Bacterial meningitis	50%
Hypoglycemia	50%
Developmental defect	0%

Treatment of Neonatal Seizures (Reference 15)



Neonatal loading doses of phenytoin or phenobarbital may be given as single 20 mg/kg doses IV over at least 20 minutes. If seizures are not controlled after 20 mg/kg of phenobarbital, additional 5 mg/kg loading doses of phenobarbital may be given up to a total loading dose of 30 mg/kg, prior to the administration of phenytoin. Serum phenobarbital concentrations should be monitored when using these higher doses. Intubation and mechanical ventilation may be required.

Let’s repeat videos