NEONATAL SEIZURES

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Incidence

- Population studies demonstrate association to birth weight
  - Less than 1500 g → 57.5 per 1000 infants
  - 2500-3999 g → 2.8 per 1000 infants

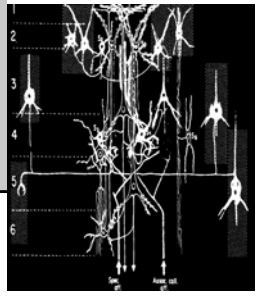
Neonatal seizures

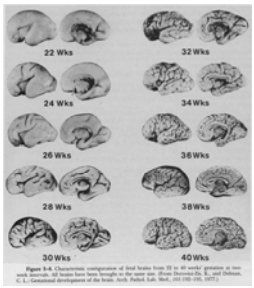
- What is a seizure in a neonate?
- Do neonatal seizures harm the brain?
- What causes neonatal seizures?
- Role of EEG in neonatal seizures
- Treatment of neonatal seizures
- Prognosis of neonatal seizures

What is a seizure?

- Clinical Definition
  - A paroxysmal alteration in neurologic function
- Electrographic Definition
  - Abnormal hypersynchronous and excessive excitation of a population of cortical neurons

Brain Development





Neonatal Seizure Classification

- Four Essential Seizure Types
  - Subtle
  - Clonic
  - Tonic
  - Myoclonic

Subtle Seizures

TABLE 5-6
Selected Major Manifestations of Subtle Seizures

Ocular phenomena
- Tonic horizontal deviation of eyes with or without jerking of eyes*
- Sustained eye opening with ocular fixation†

Oral-buccal-lingual movements
- Chewing†
- Other (see text and Table 5-7)

Limb movements
- (See text and Table 5-7)

Autonomic phenomena‡

Apneic spells*

*Documented with simultaneous electroencephalographic (EEG) seizure activity most commonly in term infants.
†Documented with simultaneous EEG seizure activity most commonly in premature infants.
‡Documented with simultaneous EEG seizure activity as a prominent isolated seizure manifestation most commonly in the premature infant, but autonomic phenomena (e.g., increase in blood pressure) are common accompaniments of seizures in term infants as well.

Classification of Neonatal Seizures

TABLE 5-5
Classification of Neonatal Seizures

	ELECTROENCEPHALOGRAPHIC SEIZURE	
CLINICAL SEIZURE	COMMON	UNCOMMON
Subtle	+*	
Clonic		
Focal	+	
Multifocal	+	
Tonic		
Focal	+	
Generalized		+
Myoclonic		
Focal, multifocal		+
Generalized	+	

*Only specific varieties of subtle seizures are commonly associated with simultaneous electroencephalographic seizure activity; see text and Table 5-6 for details.

What are not seizures?

- Jitteriness
  - Not accompanied by ocular or autonomic phenomena
  - Excessive stimulus sensitivity
  - Stopped by gentle passive flexion of limb
- Benign paroxysmal neonatal motor phenomena
- Roving, sometimes dysconjugate eye movements
- Sucking, puckering movements not accompanied by ocular phenomena
- Benign neonatal sleep myoclonus

Do neonatal seizures harm the brain?

Seizure Mechanisms in the Neonatal Brain

TABLE 5-1

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	Hypoxemia, ischemia, and hypoglycemia
Deficit of inhibitory neurotransmitter (i.e., relative excess of excitatory neurotransmitter)	Pyridoxine dependency
Membrane alteration—↑ Na^+ permeability	Hypocalcemia and hypomagnesemia

Epileptiform Changes More Readily in the Neonatal Brain from Hypoxia

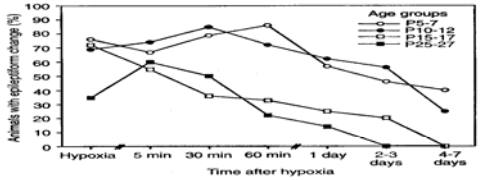


Figure 5-1 Frequency of epileptiform electroencephalographic changes in animals from four age groups sampled at 5, 30, and 60 minutes, and 1 to 7 days following O_2 deprivation. Data are represented as frequency of epileptiform change across all levels of O_2 exposure. *P* is the age in postnatal days. Note the markedly higher frequency of epileptiform changes after hypoxia in the youngest animals studied. (From Jensen FE, Applegate CD, Holtzman D, et al: *Ann Neurol* 29:629-637, 1991.)

Reduced CSF Glucose Concentration

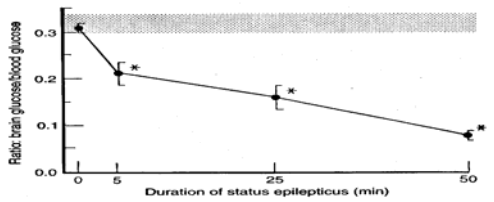


Figure 5-3 Decline in brain glucose concentration with seizure. Ratio of brain glucose to blood glucose levels in convulsing neonatal rats as a function of duration of seizure activity. *Shaded area* represents mean control values ± SE. *Asterisks* indicate difference from controls at $p < .01$. (From Wasterlain CG, Duffy TE: *Arch Neurol* 33:821, 1976.)

Reduced Energy Metabolism

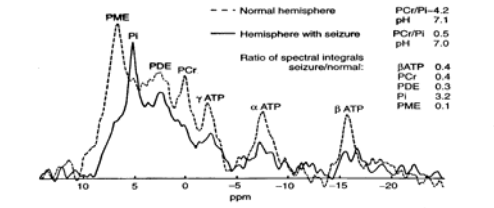


Figure 5-4 Magnetic resonance (MR) (^{31}P) spectra from a full-term infant during subtle seizure activity (oral-buccal-lingual movements, i.e., lip-smacking and chewing). The electroencephalogram demonstrated seizure activity emanating from the left temporal region. The MR spectrum from the nonictal hemisphere *(dotted line)* is normal. The spectrum from the ictal hemisphere *(solid line)* exhibits a marked decrease in phosphocreatine *(PCr)* and adenosine triphosphate *(ATP)* and a corresponding increase in inorganic phosphate *(Pi)*. *PDE*, Phosphodiesters; *PME*, phosphomonoesters. (Courtesy of Dr. Donald Younkin.)

Repeated Seizures

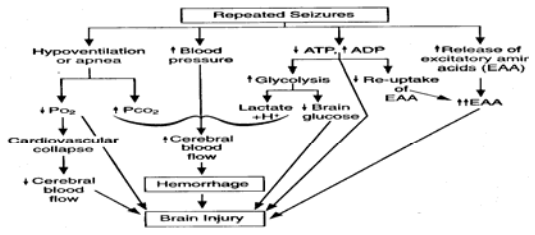


Figure 5-6 Best documented mechanisms for the occurrence of brain injury consequent to repeated seizures. See text for details. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; Po_2, oxygen pressure; Pco_2, carbon dioxide pressure.

Reduced Macromolecular Metabolism with Seizures

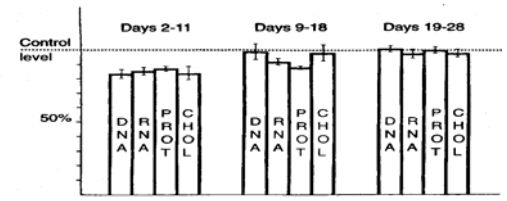
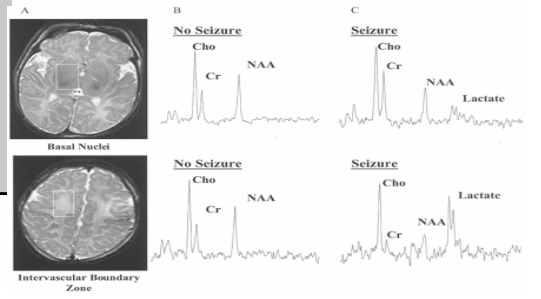


Figure 5-5 Effect of daily seizures at different ages on subsequent brain content of DNA, RNA, protein *(PROT)*, and cholesterol *(CHOL)*. Rats were sacrificed at the age of 30 days. The most significant deficits occurred in animals that were subjected to seizures at the youngest ages. (Courtesy of Dr. Claude Wasterlain.)

Perinatal Asphyxia & Seizures



Cell Counts in Hippocampus

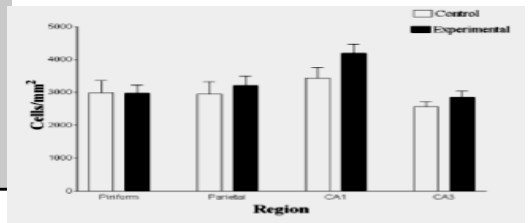
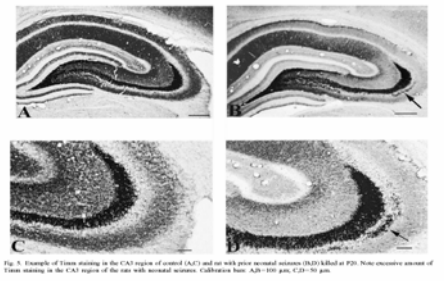


Fig. 2. Comparison of cell counts in the piriform cortex, parietal cortex and hippocampal subfields CA3 and CA1 in the controls and experimental animals with neonatal seizures. No significant differences were noted between groups at any of the four anatomical sites studied.

Sprouting in CA3



CNS Consequences

Finding	Mechanism	Immature Brain
Seizure → neuronal injury	Toxic necrosis, apoptosis	? age dependent ?less vulnerable
Hippocampual → seizure	Reorganization	?age dependent
Recurrent seizure	Deplete energy Protein & DNA synthesis	?transient
Learning / Behavior	None observed Increased emotionality	Species variable
Alter brain pathway	Interfere with cortical projection	?late function
		Mizrahi Epilepsia 1999

Systemic Consequences

- Altered cardiovascular dynamics
  - Blood pressure, heart rate, cerebral flow
- Respiratory compromise
- Changing metabolic milieu
  - Increased metabolic rate
  - Hypoglycemia, high energy P depletion
  - ?Altered fuel utilization

Causes of Neonatal Seizure

Neonatal Seizure Etiologies

TABLE 5-18

Major Etiologies of Neonatal Seizures in Relation to Time of Seizure Onset and Relative Frequency

ETIOLOGY	TIME OF ONSET*		RELATIVE FREQUENCY†	
	0-3 DAYS	>3 DAYS	PREMATURE	FULL TERM
Hypoxic-ischemic encephalopathy	+		+++	+++
Intracranial hemorrhage‡	+	+	++	+
Intracranial infection§	+	+	++	++
Developmental defects	+	+	++	++
Hypoglycemia	+		+	+
Hypocalcemia‖	+	+	+	+
Other metabolic¶	+			+
Epileptic syndromes#	+	+		+

*Postnatal age when seizures most commonly begin.
†Relative frequency of seizures among all etiologies: +++, most common; ++, less common; +, least common.
‡Hemorrhages are principally germinal matrix–intraventricular, often with periventricular hemorrhagic infarction, in the premature infant and subarachnoid or subdural in the term infant. See text concerning time of onset.
§Early seizures occur usually with intrauterine nonbacterial infections (e.g., toxoplasmosis, cytomegalovirus infection) and later seizures usually occur with herpes simplex encephalitis or bacterial meningitis.
‖Two varieties of hypocalcemia are included (see text).
¶See text for types.
#Four different syndromes are included (see text).

Epileptic Syndromes in the Newborn

- Benign familial neonatal seizures
- Benign idiopathic neonatal seizures (5th day Fits)
- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy (Ohtahara syndrome)

Role of EEG

32 EEG +; 31 EEG –
< 34 wk #3; > 37 wk #26

8- clinical and EEG +
13- subclincal (EEG +)
11- clinical and subclinical
85% no clinical behavior with EEG seizures

13% interictal period > 60 minutes

Bye

Seizure Frequency

EEG exams

Seizures/hour	9.5 (1-66)
Seizure duration	132 sec (19-675)
Longest seizure	280 sec (26-1840)
% EEG with sz	23% (2-87)

Clancy

EEG & Seizures

Characteristics	Asphyxia	Stroke	p (A vs S)
Esz/infant #	113 (4-922)	9 (3-94)	.007
Time in sz, hr	2.4 (.27-30.5)	.25 (.13-2.3)	.004
Average time, sec	93 (17-651)	98 (77-299)	
Longest, min	7 (.8-32)	3.1 (2.2-10)	
Status, #, %	11 (48)	1 (14)	
Esz, PB/ Phy, %	7 (30)	1 (14)	

McBride 2000

EEG Background Activity

EEG background as predictor of electrographic seizures in high-risk neonate *Laroia N. Epilepsia 1998; 39:545*

High risk infants
EEG monitoring onset @ 24 hours (>3 hours-days)
Asphyxia 40/51; 14 with clinical seizures
Monitoring time prior to first seizure (~10 minutes- 21 hours)

EEG background and occurrence of electrographic seizures

Retrospective and prospective groups combined (n = 51)	*Normal or immature EEG background*	*Abnormal EEG background*
No electrographic seizures	23	5
Electrographic seizures	1	22

Treatment of Neonatal Seizures

Acute Therapy

- Glucose
  - 10% solution
  - 2ml/kg
- Phenobarbital
  - 20mg/kg IV, boluses as necessary up to 40mg/kg
- Calcium gluconate 5% soln, 4mk/kg, IV
- Mg sulfate 50% soln, 0.2ml/kg, IM
- Pyridoxine 50-100mg, IV

AED Treatment

- 59 neonates with EEG seizures
- Randomized; PB (25µg/ml); Phy (3µg/ml)
- Control
  - PB 43%, Phy 45%, combined 57-62%
- Seizure severity (freq, duration)
  - Inversely related to control

▪ Painter et al, N Engl J Med 1999; 341(7):485

Alternative Therapies

IV

- Diazepam, lorazepam, midazolam
- Clonazepam, lidocaine, paraldehyde

PO

- Carbamazepine, valproate, vigabatrin
- Primidone, levetiracetam

Prognosis of Neonatal Seizures

Prognosis – Age and EEG

TABLE 5-25

Prognosis of Neonatal Seizures—Relation to Maturity

MATURITY	OUTCOME		
	NORMAL	DEAD	SEQUELAE
Term (>2500 g)*	60%	19%	21%
Premature (<2500 g)*	35%	37%	28%
Premature (<1500 g)†	19%	58%	23%

*Data from personal experience (100 term and 80 premature [<2500 g] infants and from Andre M, Matisse N, Vert P, et al: *Neuropediatrics* 19:201-207, 1988 (45 term and 26 premature infants) and Scher MS, Aso K, Beggarly ME, et al: *Pediatrics* 91:128-134, 1993 (30 term and 62 premature infants).
†Data from Watkins A, Szymonowicz W, Jin X, et al. *Dev Med Child Neurol* 30:162-169, 1988 (65 infants) and van Zeben ADM, Verloove-Vanhorick SP, den Ouden L, et al: *Neuropediatrics* 21:62-65, 1990 (72 infants).

TABLE 5-26

Prognosis of Neonatal Seizures—Relation to Electroencephalogram (EEG)*

EEG BACKGROUND	NEUROLOGICAL SEQUELAE (%)
Normal	≤10
Severe abnormalities†	≥90
Moderate abnormalities‡	~50

*Based primarily on data reported by Rowe JC, Holmes GL, Hafford J, et al: *Electroencephalogr Clin Neurophysiol* 60:183-196, 1985; Lombroso CT: In Wasterlain CG, Treeman DM, Porter R, editors: *Advances in neurology*, New York, 1983, Raven Press; and includes both full-term and premature infants.
†Burst-suppression pattern, marked voltage suppression, and electrocerebral silence.
‡Voltage asymmetries and "immaturity."

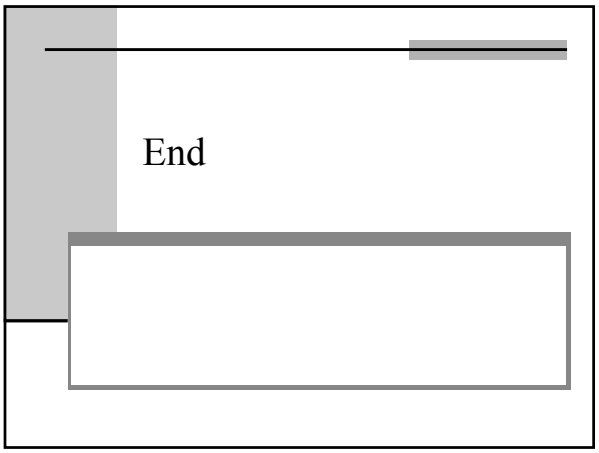
Prognosis - Disease

TABLE 5-27

Prognosis of Neonatal Seizures—Relation to Neurological Disease

NEUROLOGICAL DISEASE*	NORMAL DEVELOPMENT (%)†
Hypoxic-ischemic encephalopathy	50
Intraventricular hemorrhage‡	10
Primary subarachnoid hemorrhage	90
Hypocalcemia	
Early onset	50§
Later onset	100#
Hypoglycemia	50
Bacterial meningitis	50
Developmental defect	0

*Prognosis is for those cases with the stated neurological disease when seizures are a manifestation (thus value usually will differ from *overall* prognosis for the disease).
†Values are rounded off to nearest 5%.
‡Usually severe intraventricular hemorrhage associated with major periventricular hemorrhagic infarction.
§Represents primarily the prognosis of complicating illness; prognosis approaches that of later onset hypocalcemia of the nutritional type if no or only minor neurological illness present.
#Later onset hypocalcemia of the nutritional type.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