NEONATAL SEIZURES

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Neonatologist

	* neonatal	* pediatrics.
* most common type	subtle [Tonic-clonic] the least common	tonic-clonic
	↓	↓
*prognosis for tonic-clonic.	poor prognosis	good prognosis
*mc cause.	the least cause: idiopathic	idiopathic
*duration of treatment.	1 month	2 years at least.

* most common age group present with convulsion → neonate.
[because any change in pediatric age group can be presented as: convulsion]
*most common type of convulsion in pediatrics + adult ? tonic-clonic.
* But tonic-clonic is the most rare in neonatal age group.
* tonic clonic in adult and pediatrics carry good prognosis but extremly bad prognosis in neonatal age group

* in pediatrics + adult the most common cause is → idiopathis (but in neonatal is the least cause).
* in pediatrics the treatment at least 2 years, but in neonatal for 1 month.
and diazepam is avoided in neonate

Definition

- A seizure is a paroxysmal behavior caused by hypersynchronous discharge of agroup of neurons caused altered neurologic function :
  - ✓ behavior
  - ✓ motor 4 types , the most common type: suble تشنجات خفية.
  - ✓ and/or autonomic function

↳ هلق تحكي فقط في convulsions.

*twitching of the mouth

*recurrent apnea + cyanosis

*apnea, cyanosis, bradycardia → convulsion

*in neonatal age group ddx according to the age.

Definition

- Neonatal period limited to :
  - first 28 days for term infants
  - 44 weeks gestational age for pre-term

Frequency

- Incidence of seizures *higher in the neonatal period* than in any other age group
- In US – incidence has not been established clearly
- Estimated frequency of 80-120 per 100,000 neonates/year
- 1-5:1000 live births
- neonatal seizures have unusual presentations

Why do neonatal seizures have such unusual presentations?

anatomical immaturity.
physiological immaturity

Subtle type mainly not gross motor presentation.

- Immature CNS cannot sustain a synchronized, well orchestrated generalized seizure

Usually:-
*Hypersynchronic electrical discharge at the motor cortex it will be transmitted to the muscles → Contraction
*but in neonate → immature CNS. So, cant propagate the electrical

discharge from the deep structures of the brain to the cortex.

Perinatal Anatomical and Physiological Features of Importance in Determining Neonatal Seizure Phenomena

① * **ANATOMICAL**

- **Synaptogenesis** not complete
- **Deficient myelination** in cortical efferent systems

* عشان تنتقل discharge من deep structures لـ cortex :لازم

✓ 1. good synaptogenesis.

✓ 2. good melanin sheath

ex: Jeterines.

Perinatal Anatomical and Physiological Features of Importance in Determining Neonatal Seizure Phenomen

② PHYSIOLOGICAL

①

- In limbic and neocortical regions— excitatory synapses **develop before** inhibitory synapses (↑ N-methyl-D-aspartate receptor activity, gamma-aminobutyric acid excitatory)

*relative increase of excitatory neurotransmitter comparing to the inhibitory (mainly GABA)

- Immature hippocampal and cortical neurons **more susceptible to seizure activity** than mature neurons

③

- Deficient development of **substantia nigra system** for inhibition of seizures

↳ main inhibitory system in the brain

- **Impaired propagation of electrical seizures**, and synchronous discharges recorded from surface electroencephalogram may not correlate with behavioral seizure phenomena

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

Classification of Neonatal Seizures

* لانه مش كل الحالات epilepsy كذلك لازم نفيز.

- ✓ **Clinical**
  - * subtle
  - * tonic
  - * clonic
  - * myoclonic
- ✓ **Electroencephalographic**
  - ✓ epileptic
  - ✓ non-epileptic.

Classification

I. Clinical Seizure

- Subtle → mc type. , good prognosis.
- Tonic → المريض تخشب.
- Clonic
- Myoclonic (very bad in neonate)
- Tonic clonic → most rare in neonatal age group

Classification

* Treatment with anti-epileptic should be with abnormal (EEG)

II. Electroencephalographic seizure (eeg).

- ✓ Epileptic
- ✓ Non-epileptic (Jefferiness)

Clinical Classification

1. **Subtle** => Good prognosis.

- More in preterm than in term
- Eye deviation (term)
- Blinking, fixed stare (preterm)
- Repetitive mouth and tongue movements — twitching of the mouth.
- Apnea
- Pedaling and tonic posturing of limbs

*recurrent cyanosis.

Clinical Classification

2. Tonic ⟹ extension

* → decerebrate
* → decorticate

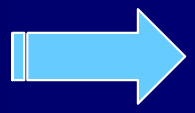
- ✓ Primarily in Preterm
- ✓ May be focal or generalized
- Sustained extension of the upper and lower limbs (mimics decerebrate posturing)
- Sustained flexion of upper with extension of lower limbs (mimics decorticate posturing)

  ⇨ Signals severe *ICH in preterm infants* (bad prognosis)

Clinical Classification

3. **Clonic** => extension + Flexion.

- Primarily in term
- Focal or multifocal
- Clonic limb movements
- Consciousness may be preserved



Signals focal cerebral injury

meningitis

Clinical Classification

* in adult → good prognosis (زي لما الرجل تنتش اثناء النوم)

4. Myoclonic

- Rare
  → Contraction of the distal part of the neuron.
- ✓ Focal, multifocal or generalized
- Lightning-like jerks of extremities (upper > lower)

✓ * extremly bad prognosis in pediatric age group.
  → ex: West syndrom [salam attack]
  → associated with tubular sclerosis
  .HIE عادة في 50٪ من

Summary of Seizure Types

Seizure type	*Occurs in*	*Clinical signs*
Subtle	Preterm and Term	Eye deviation (Term) Blinking, fixed stare (Preterm) Repetitive mouth & tongue movements * twitching of mouth. Apnea Pedaling, tonic posturing of limbs
Tonic	Primarily Preterm	May be focal or generalized Tonic extension or flexion of limbs (often signals severe ICH in preterm infants)
Clonic	Primarily term	May be focal or multifocal Clonic limb movements (synchronous or asynchronous, localized or often with no anatomic order to progression) Consciousness may be preserved Often signals focal cerebral injury.
Myoclonic	Rare	Focal, Multifocal, or Generalized Lightning-like jerks of extremities (upper>lower)

Electroencephalographic seizure

I. Epileptic

- Consistently associated with electro-cortical seizure activity on the EEG
- Cannot be provoked by tactile stimulation
- Cannot be suppressed by restraint of involved limb or repositioning of the infant
- Related to hypersynchronous discharges of a critical mass of neuron

Electroencephalographic seizures

II. Non-epileptic

Jitteriness. → 95% Idiopathic and normal
→ 5% due to hypoglycemia and hypocalcemia

- No electro-cortical signature
- ✓ Provoked by stimulation
- Suppressed by restraint or repositioning
- Brainstem release phenomena (reflex)

* doesn't associated with eye manifestation
* EEG → normal.

	Non-Epileptic	Epileptic
stimulation (tactile)	provoke	not Provoked
suppression by resistance	yes (tremor-like)	no
Eye	normal	deviation
EEG !!!	normal	abnormal
Autonomic	none	Bradycardia, Cyanosis, MA, ...

- Non-Epileptic → Phases are equal
يعني مثل ال Fine Tremor ... اللي تنقبض بالاتجاهات بشكل متساوي

* elinical Manifestation should be distinguish between them More Important

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 associate with simultaneous Electroencephalographic seizure activity.

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

Does absence of EEG seizure activity indicate that a clinical seizure is non - epileptic?

- Certain clinical seizures in the human newborn originate from electrical seizures in deep cerebral structures (limbic regions), or brain stem structures and thereby are either not detected by surface-recorded EEG or inconsistently propagated to the surface

Differentiation of Seizures from Nonconvulsive Movements

Jitteriness Versus Seizure

CLINICAL FEATURE	JITTERINESS	SEIZURE
Abnormality of gaze or eye movement	O	+
Movements exquisitely stimulus sensitive	+	O
Predominant movement	Tremor	Clonic jerking
Movements cease with passive flexion	+	O
Autonomic changes	O	+ → cyanosis bradycardia.

1. Pregnancy history
2. Delivary history
3. postnatal history
4. FH

Etiology

① * ddx of convulsion at first minutes?
1) HIE
2) anesthesia. (local) → injection of lidocaine at the scalp
↳ * bradycardic
* mydriasis
3) Brain malformation
4) Sever ICH

- **Pregnancy history** ①
  - → Search for history that supports TORCH infections
  - → History of fetal distress, preeclampsia or maternal infections

② ddx at 1 hour → *hypoglycemia.
③ after 24 hours → sepsis +meningitis.

④ 3 days → early type of hypocalcemia [bad prognosis]

⑤ 4 days → late hypocalcemia + hypomagnisemia.

⑥ 5 days → subarachnoid hemorrhage /benign familial convulsions.

Etiology

- **Delivery history**
  - Type of delivery
  - Apgar scores offer some guidance
  - Low Apgar score without the need for resuscitation and subsequent neonatal intensive care is unlikely to be associated with neonatal seizures

Etiology

- **Postnatal history**
  - Neonatal seizures in infants without uneventful antenatal history and delivery may result from postnatal cause
  - Tremulousness may be secondary to drug withdrawal or hypocalcemia
  - Temperature and blood pressure instability may suggest infection

Etiology

- **Family history**
  - may suggest genetic syndrome
  - Many of these syndromes are benign
  - In the absence of other etiologies, family history of seizures may suggest good prognosis

Benign familial neonatal seizures, an autosomal dominant

- begins on the 2nd–3rd day of life
- with a seizure frequency of 10-20/day.
- Patients are normal between seizures
- stop in 1–6 mo

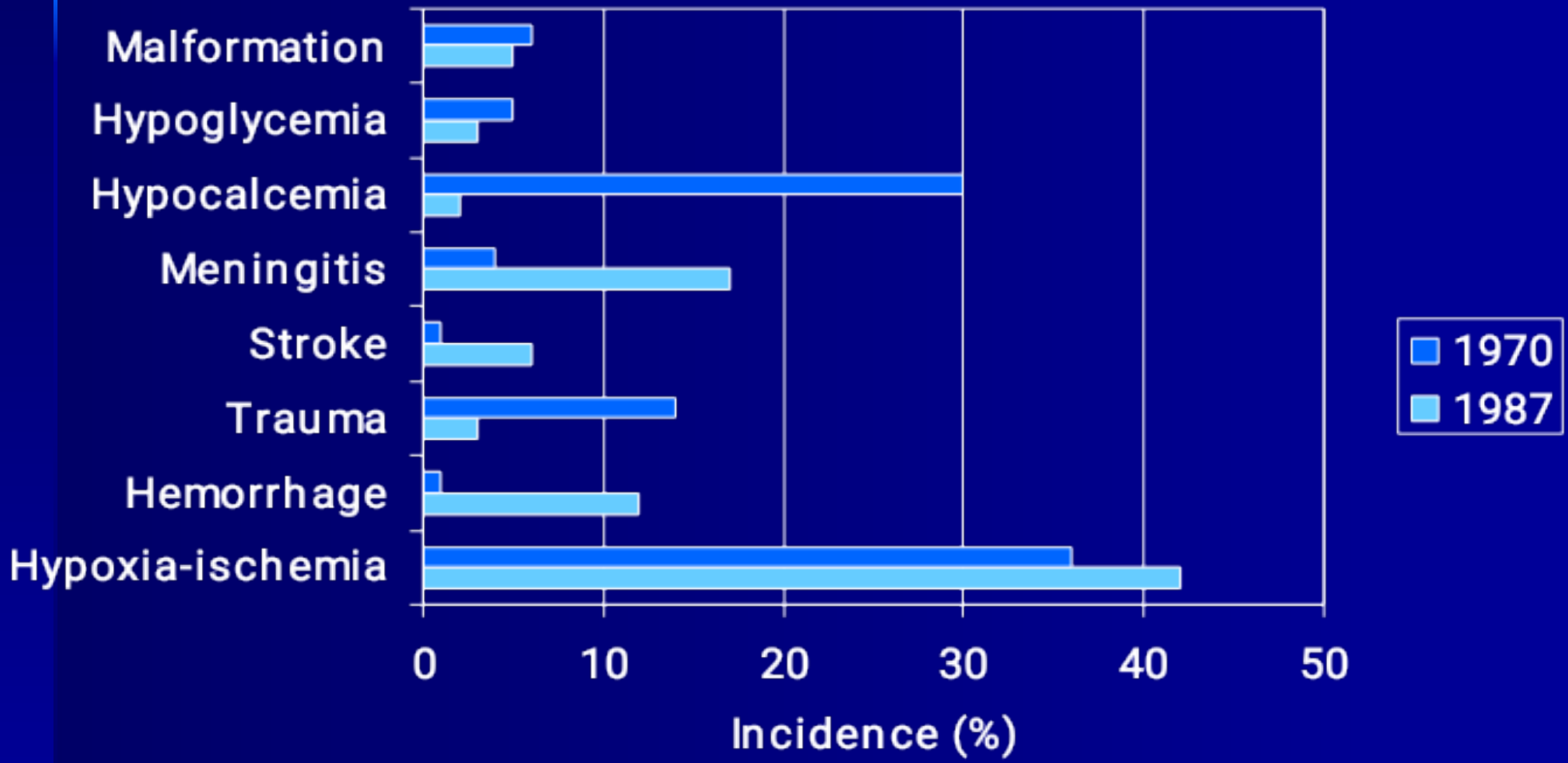
Major Etiologies of Neonatal Seizures in Relation to Time of Seizure Onset and Relative Frequency

MAJOR CAUSES OF NEONATAL SEIZURES: Several causes often coexist!

Cause	*Usual Age at Onset*	*Preterm*	*Term*
Hypoxic-ischemic encephalopathy	<3 days	+++	+++
Metabolic			
Hypoglycemia	<2 days	+	+
Hypocalcemia			
Early-onset bad Prognosis (Metabolic disorder)	2–3 days	+	+
Late-onset good Prognosis (Nutritional etiology)	>7 days	+	
Hypomagnesemia (often with Hypocalcemia)			
Hyper/Hyponatremia			
Drug Withdrawal	<3 days	+	+
Local Anesthetic Toxicity			
Pyridoxine (Vitamin B6) Dependency			
Disorders of Small Molecules (Amino Acid, Organic Acid &Urea Cycle Disorders)			
Disorders of Subcellular Organelles (Mitochondrial & Peroxisomal Disorders)			
Intracranial infection	<3 days	++	++
Bacterial meningitis (E. coli, Group B Strep, Listeria)			
Viral Encephalitis (Herpes Simplex, Enterovirus)			
Intrauterine Infection (CMV, Toxoplasm., HIV, Rubella, Syphilis)	>3 days	+	+
Cerebral Vascular			
Intraventricular hemorrhage	<3 days	++	
Primary subarachnoid bleed	<1 day		++
Subdural/epidural hematoma			
Focal Ischemic Necrosis (Stroke)	Variable		++
Sinus Thrombosis	Variable		+
Developmental defects	Variable	++	++
Neurocutaneous Disorders (Tuberous Sclerosis Complex, Incontinentia Pigmenti)			
Epilepsy Syndromes			
Epileptic Encephalopathies (Early Myoclonic Encephalopathy, Early Infantile Epileptic Encephalopathy)			
Benign Familial Neonatal Convulsions			

(Relative Frequency: +++ = most common; ++ = less common; + = least common. If no +, then uncommon.)

Comparison of prominent etiologic diagnoses of seizures in the newborn period.



Fanaroff A, Martin R.Neonatal seizures. In:Neonatal and Perinatal Medicine, Diseases of the Fetus and Infant,6th ed

Inborn Errors of Metabolism Associated With Neonatal Seizures

*any inborn errors can presents with convulsions → Screening: ammonia + lactate + blood gas.
because they have: metabolic alkalosis, hyperammonia, due to lactate accumulation.

Conditions That Have a Specific Treatment

- Pyridoxine (B6) dependency
- Folinic acid-responsive seizures
- Glucose transporter defect
- Creatine deficiency

Other Conditions

- Nonketotic hyperglycinemia
- Sulfite oxidase deficiency
- Molybdenum cofactor deficiency (combined deficiency)
- Carbohydrate-deficient glycoprotein disorder
- Lactic acid disorders
- Mitochondrial disorders
- Maple syrup urine disease
- Isovaleric acidemia (sweaty feet, cheesy odor)

* in pediatric age group most of them no need for workup.

Laboratory Studies to Evaluate Neonatal Seizures

* in neonate you have to investigate any case. because usually there's underlying cause.

Indicated

- Complete blood count, differential, platelet count
- Urinalysis and BUN
  - These tests rule out posthypoxic renal dysfunction; hypoxic damage to multiple organ systems may also be suggested by elevated liver transaminase levels.
- Blood glucose (Dextrostix),
- Ca, P, Mg, electrolytes
  - Transient neonatal hypocalcemia is a cause of neonatal seizures during the first 3 weeks of life; hypocalcemia associated with chromosome 22q11 deletion syndrome may also be a consideration
- Blood oxygen and acid-base analysis
- Blood, CSF and other bacterial cultures

① CBC to rule out sepsis. [septic workup]

② urine analysis → hematuria may indicate HIE → multiorgan dysfunction.

③ blood glucose

→ to rule out meningitis.

Laboratory Studies to Evaluate Neonatal Seizures

- **Cerebrospinal fluid analysis**
- This should include tests checking for the following:
  - Pleocytosis
  - Xanthochromia - Suggestive of blood breakdown products, particularly if jaundice is not present
  - Lactic acid and pyruvate - For evidence of mitochondrial cytopathies
  - Herpes virus - Using a polymerase chain reaction (PCR) assay
  - Glucose concentration - Low glucose concentration is suggestive of bacterial meningitis

Laboratory Studies to Evaluate Neonatal Seizures

Clinical Suspicion of Specific Disease

Serum immunoglobulins, TORCH antibody titers, and viral cultures

Blood and urine metabolic studies (bilirubin,ammonia, lactate, reducing substance.)

Blood and urine toxic screen

Blood and urine amino and organic acid screen

Imaging Studies

- **Cranial ultrasonography**
  - it is a valuable tool for quickly ascertaining whether intracranial hemorrhage, particularly intraventricular hemorrhage, has occurred.
- **Cranial CT scanning**
  - much more sensitive tool than ultrasonography in detecting parenchymal abnormalities.
  - can delineate congenital malformations. Subtle malformations may be missed on CT scan, requiring a magnetic resonance imaging (MRI) study.
- **MRI**
  - Cranial MRI is the most sensitive imaging study for determining the etiology of neonatal seizures, particularly when electrolyte imbalance has been excluded as the seizures' cause

*at the open anterior Fontanel.
*not invasive *rapid screen *without SE.
*sensetive if patient have intraventricular Hemorrhage.
or periventricular — [PVL]
Gold standard
Can invistigate the subtle type.
LOW neonatal ↓ in MRI ↓ *
↑ risk of hypoxia ← anesthesia

Treatment

→ glucose [First step]
if hypoglycemia indication of IV bolus. 2-4 ml.

- Ensure adequate ventilation and perfusion.
- Correct metabolic disturbances :
  - ✓ hypoglycemia - (10% glucose in water) 4 mL/kg IV (0.4 g/kg) as bolus. Follow with continuous infusion at up to 8 mg/kg/min IV
  - ✓ hypocalcemia - (calcium gluconate 10%) 100mg/kg IV over 10 minutes (**Note**: Monitor cardiac rhythm for bradycardia) Follow with maintenance of 500 mg/kg/24 hrs IV or PO
  - hypomagnesemia- *Hypomagnesemia*: (magnesium sulfate) 25-250 mg/kg/dose IV/IM → IM better
  - pyridoxine deficiency- Pyridoxine100–200 mg
  - meningitis- initiation of antibiotics

* dose: 75 mL
if no response check mg
⇓
metabolisim of calcium

* in primary pulmonary hypertension give IV [slowly]

Treatment AED

- only after adequate ventilation and perfusion have been established and the blood glucose concentration has been measured
- To minimize brain damage
- Some controversy when to start anticonvulsants : If seizure is
  - prolonged (longer than 3 minutes),
  - frequent
  - or associated with cardiorespiratory disturbance

Drug Therapy For Neonatal Seizures

Standard Therapy

① phenobarbital if not respond add phenytoin if not respond add Lorazepam → the general anesthesia.

AED	Initial Dose	Maintenance Dose	Route
Phenobarbital	20mg/kg	3 to 4 mg/kg per day	IV, IM, PO
Phenytoin	20 mg/kg	3 to 4 mg/kg per day	IV, PO[a]
Lorazepam[2]	0.05 to 0.1 mg/kg	Every 8 to 12 hours	IV
Diazepam[2´]	0.25 mg/kg	Every 6 to 8 hours	IV

① * 1st line ← Phenobarbital

binding [illegible] of albumin [illegible] therapeutic range [illegible]

Diazepam → can induce Kernicterus . [illegible] ✓

AED= andtiepileptic drug; IV= intravenous; IM= intramuscular; PO= oral

[a]Oral phenytoin is not well absorbed.

[2]Benzodiazepines typically not used for maintenance therapy.

[3]Lorazepam preferred over diazepam.

② * can given IV, IM, oral.

③ * any convulsion occur with it : local metabolic acidosis → ↑ brain permiability for phenobarbital

④ in HIE patient → improve the prognosis (double the dose).

↓ metabolism of the brain ↓

Acute therapy of neonatal seizures

- If with hypoglycemia- Glucose 10%: 4ml/k IV
- If no hypoglycemia-
  - Phenobarbital:20mg/k IV loading dose
  - Phenytoin: 20 mg/kg, IV (1 mg/kg/min)
  - Lorazepam:0.05-0.10 mg/kg, IV

Pharmacological properties of Phenobarbital

- Enters the CSF rapidly with high efficiency
- The blood level is largely predictable from the dose administered
- It can be given IM or IV (more preferred)
- Maintenance therapy accomplished easily with oral therapy
- Protein binding lower in newborn—free levels of drug are higher
- Entrance to the brain increased by local acidosis associated with seizures

Alternative Antiepileptic Drugs (AED) for Neonatal Seizures

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
- 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
- Dexamethasone: 0.6 to 2.8 mg/kg
- Pyridoxine (B6): 50 to 100 mg, then 100 mg every 10 minutes (up to 500mg)

Alternative AEDs for Neonatal Seizures

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
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

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Determinants of Duration of anticonvulsant therapy for neonatal seizures

- Neonatal neurological examination
- Cause of neonatal seizure
- Electroencephalogram

يرجع لحجمه بعد شهر لذا
كان كويس يوقف عنده
anti-epileptic drug.
if abnormal:
stop phenytoin
and still use
Phenobarbitone

Duration of anticonvulsant therapy-Guidelines

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

Duration of anticonvulsant therapy-Guidelines

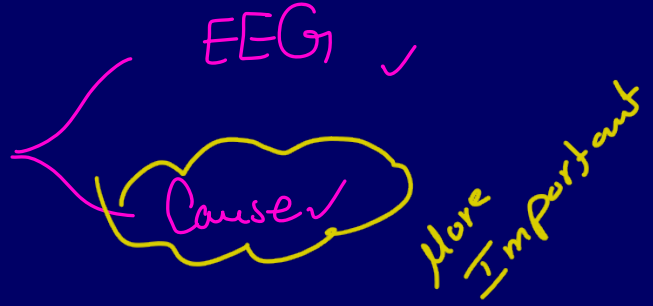
One month after discharge

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

* After 1 Month :-
If EEG Abnormal and Neurological exam Normal {stop Phenobarbital}
If EEG Normal and :. : abnormal {also stop Phenobarbital}

[Normal EEG] ممكن يكون abnormal Electrical discharge بتشتغل على [Phenobarbital] فنوقف

Prognosis



Two most useful approaches in utilizing outcome

- EEG
- Recognition of the underlying neurological disease

[Cause]

Prognosis of Neonatal seizures in relation to 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.”

Causes of Neonatal Seizures and Outcomes

Cause	Percent of Patients Who Have Normal Development
Hypoxic-ischemic encephalopathy	50
Intraventricular hemorrhage	10
Subarachnoid hemorrhage	90
Hypocalcemia	
Early-onset	50
Later-onset	100
Hypoglycemia	50
Bacterial meningitis	50
Developmental malformations	0
Benign familial neonatal convulsions	~100
Fifth-day fits	~100

Complications

- Cerebral palsy
- Hydrocephalus
- Epilepsy
- Spasticity (from hypoxia)
- Feeding difficulties

Thank You

10.What's the cause of neonatal seizure that associates w/ the BEST outcome:

- **A. HIE.**
- **B. Hypoglycaemia.**
- **C. LATE-onset hypocalcaemia. XXXX**
- **D. Early onset hypocalcemia**
- **E. Bacterial meningitis**

54-Neonatal seizures include all these seizures types except

a. Subtle

b. Clonic

c. Tonic-clonic

d. Myoclonic

e. Tonic

3. concerning treatment of neonatal seizures all the following are true except:

- phenobarbital can be given im or IV
- phenobarbital enters the CSF rapidly with high efficiency
- phenobarbital treatment should be continuing for two year in neonatal seizures✔
- the blood level of phenobarbital is largely predictable from the dose administrated.

94 - The drug of choice for neonatal seizure is:

a. carbamazepine
b. valproic acid
c. phenobarbitone
d. midazolam
e. phynetoin

51-Finding associated with bad prognosis in neonatal seizures ?
early hypocalcemia

3. regarding neonatal seizures, all statements are true except :

- **incidence is more in premature babies than in full term babies.**
- **the subtle type is the commonest.**
- **jitteriness is the main differential diagnosis.**
- **if underlying cause is hypoglycemia the outcome is excellent. XXXX**
- **phenobarbitone is the drug of choice.**

5- Wrong regarding Neonatal seizure :
subtle type is more in term than pre-term ??