

HYPOXIC ISCHEMIC ENCEPHALOPATHY

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Learning Objectives

- HIE: Definition, clinical presentation & management.
- Pathophysiology and *newer proposed interventions*.
- Prognostic factors.

HIE: Definition

AAP & ACOG

- Neonatal Encephalopathy (Seizures, coma , hypotonia, lethargy, posturing)
- with umbilical art.pH < 7.00
- AND 5 min. APGARS 3 or less.
- AND multiple end organ damage.

CLINICAL

- Incidence 2-4/1000 births.
- Can be lethal-Mortality 20-50%(in severe HIE)
- 25% permanent neuropsychological handicaps:CP±MR,learning disabilities,epilepsy.

Clinical

- Maternal Factors:
Hypertension, Diabetes, Hypoxia ,
hypotension & infection. Placental
abruption, infarction, cord accidents.
- Cord pH and base excess.
- APGARS: poor predictors of outcome.

CLINICAL MANIFESTATIONS

- **ENCEPHALOPATHY :**
SEVERITY- SARNAT & SARNAT STAGING.
SIGNIFICANCE: Stage 3 or >7 days of Stage 2 is associated with poor prognosis.
- **SEIZURES.**
- **CEREBRAL EDEMA.**
- **Hemorrhage.**

Neuropathological lesions and investigations

- Selective Neuronal Necrosis
- Parasagittal Cerebral Injury
- Focal and multifocal ischemic brain necrosis.
- Periventricular Leukomalacia

Neuropathological lesions and investigations

- **U/S**: injury to basal ganglia , thalamus, PVL, focal/multifocal ischemic necrosis.
- **CT**: Severe selective neuronal necrosis, injury to basal ganglia & thalamus, PVL
- **Diffusion weighted MRI**: loss of G-W diff, Cortical highlighting, basal ganglia high signal.
- **EEG**: *Isoelectric Or Burst Suppression pattern OR abnormality persisting >12 days - POOR PROGNOSIS.*

Differential diagnosis

- SEPSIS, MENINGITIS.
- Sedation.
- Neuro-Muscular diseases.
- Birth Trauma.
- METABOLIC ENCEPHALOPATHIES.

Other systems involved

- ATN (50%)
- CARDIOMYOPATHY (25%)
- PPHN, MAS, pulmonary edema-(23%)
- HEPATIC NECROSIS
- NEC
- SIADH
- ADRENAL INSUFFICIENCY

Work up

- **Indicated**

- C.B.C., Urinalysis
- Blood glucose, BUN, creatinine, electrolytes, calcium, phos, mag.
- LFT's, enzymes (CPK, ALT, LDH)
- Blood gases
- Blood/CSF cultures
- L.P./CSF analysis
- CXR
- U/S, CT, or MRI
- EEG

- **Elective**

- S. immunoglobulins and TORCH antibody studies (also HIV)
- Viral Cultures
- U-tox, metabolic studies
- Skull and spine radiographs

Management (General Principles)

- Ensure physiological oxygen and acid base balance.
- Correct caloric, fluid, and electrolyte disturbances
- Maintain blood volume and homeostasis
- Maintain thermo neutral environment
- Treat infections.

Management

- Maintenance of adequate Ventilation

Avoid

Hypoxemia: Neuronal and white matter injury, Pressure passive circulation .

Hyperoxia: Neuronal injury,ROP.

Hypercarbia(marked): Cerebral vasodilatation,intracranial steal,Cerebral acidosis.

Hypocarbia: Diminished cerebral blood flow-ischemic injury.

Management

- Maintain Adequate Perfusion.

Recognition of pressure –passive cerebral circulation.

Avoid Systemic Hypotension/Hypertension.

Avoid Hyperviscosity.

Management

- Maintenance of Adequate Glucose levels.

Hypoglycemia: may cause neuronal injury

Marked Hyperglycemia: may provoke hemorrhage or worsen cerebral lactic acidosis.

Management

- Control of seizures.
- Prevention of fluid overload.
- Minimize hyperbilirubinemia.

Pathophysiology and new interventions.

HYPOXIC ISCHEMIC ENCEPHALOPATHY

- **Hypoxia/Anoxia**- *Partial/ total lack of O₂ in blood .*
- **Ischemia**: *Low perfusion: In fetus arises from antecedent systemic hypoxia-acidosis leading to CVS depression (or from occlusive vascular disease).*
- **Asphyxia**: *Hypoxia + Hypercapnia + Acidosis.*

Energy Failure

- **Systemic Hypoxia + Cerebral Ischemia**

= Low O₂ and Low glucose => Anaerobic glycolysis

⇒ ATP depletion and lactic acidosis

Cellular Mechanisms of Brain Injury

1. **Initiating role of Energy Failure.**
2. **Accumulation of Cytosolic Ca⁺⁺**
3. **Free Radical formation.**
4. **EXCITATORY Amino Acids .**
5. **Role of Inflammation-Cytokines.**

Energy Failure

1. ATP Depletion, Lactic acidosis.
2. Na-K+ Pump failure.
3. Cellular edema (Cytotoxic) and membrane depolarization.

Accumulation of Cytosolic Ca⁺⁺

1. Failure of energy dependent Ca⁺⁺ pumping mechanism.
 2. Opening of voltage dependent Ca⁺⁺ channels(due to depolarization).
 3. Activation of glutamate receptors.
- Ca⁺⁺ Activates:
Phospholipases,proteases,neucleases,NO synthetase,Xanthine Oxidase.
 - Also causes:
Neurotransmitter release (Glutamate,cathecholamines) ,
uncoupling of oxidative phoshorylation.

Free Radicals

- Mitochondrial electron transport system
- Arachidonic Acid
- Xanthine Oxidase on Xanthine and Hypoxanthine.
- Auto Oxidation of catecholamines
- Infiltrating neutrophils/microglia

- Cause :Lipid peroxidation,Damage to DNA,Activation of proapoptotic genes.

Excitatory Amino Acids.

- Glutamate receptors: NMDA, AMPA, Kainate, ACPD
- Ca^{++} entry, Na^+ entry, mobilization of Ca^{++} from mitochondria.
- Na^+ Leads to cell swelling and immediate cell death.
- Ca^{++} influx leads to delayed cell death.

Role of Inflammation-Cytokines.

- Microglial activation after hypoxia ischemia
- Increase in IL-1 beta and TNF- alpha.
- CSF IL-6 level correlates with severity of brain injury.

Potential Interventions

- Decrease energy depletion :
Hypothermia, barbiturates, (Mild) Hypercapnia.
- Inhibition of glutamate release: Calcium Channel blockers, Mg⁺⁺, Hypothermia, Lamotrigine/Phenytoin.
- Amelioration of impairment in Glutamate uptake:
Hypothermia.
- Glutamate receptor blockers
(Mk-801, Mg⁺⁺, Ketamin)

Potential Interventions

- Blockade of Downstream Intracellular events:

Hypothermia.

Free radical synthesis inhibitors

(allopurinol, indomethacin, iron chelators, Mg⁺⁺), Free radical scavengers (Vitamin E, 21-aminosteroids).

Interventions under investigation

Hypothermia:Gunn et al :Selective head cooling in newborn infants after perinatal asphyxia:a safety study. Pediatrics: 102:885-892,1998.

- NICHD sponsored Phase 3 trail for safety of mild hypothermia.

Predictors of Outcome

- Fetal assessment:
Biophysical profile (*Manning et al.*)
Meconium, heart rate monitoring, Blood acid-base analysis.
- APGARs
- Onset of respiration
- Neonatal neurological exam
- Neuroimaging
- EEG

Fetal acidemia & neonatal encephalopathy

- **Low JA et al; Am J Obstet Gy 177: 1391-1394, 1997**

NEONATAL ENCEPHALOPATHY	UMBILICAL ARTERIAL BASE DEFICIT		
	4-12mmol/L (n=116)	12-16mmol/L (n=58)	>16 mmol/L (n=59)
<i>NONE</i>	89%	72%	39%
<i>MINOR</i>	10%	19%	20%
<i>MODERATE</i>	1%	7%	29%
<i>SEVERE</i>	0%	2%	12%

Predictors of Outcome: APGARs

- 1-5 min APGARs
low sensitivity in predicting long term neurological outcome.
- Inter-observer variability.
- All five factors given equal weight.
- Other causes of low APGARs

APGAR scores & Mortality/ C.P.

Nelson KB et al :Pediatrics ,1981 for infants>2501g.

Extended APGAR score.Evaluated 39 term with 20 min APGARS 3 or less,6 died early,19 late and of the 14 survivors 8 had C.P. at 7 years of Age.

APGAR 0-3	DEATH first year (%)	CP in Survivors (%)
1 min	3	1
5 min	8	1
10 min	18	5
15 min	48	9
20 min	59	57

Predictors of Outcome: Onset of respiration.

- Mulligan and colleagues-19% immediate mortality and 18% morbidity among 39 patients with delayed onset of spontaneous resp(>1 min).
- D'Souza et al. *Followed 15 babies with >10 min apnea at birth, for 5 yrs. 2 had severe deficit, 5 had delayed language development. >30 min apnea survivors had universally severe damage.*

Predictors of outcome: Encephalopathy

- Neonatal neurological syndrome –single most useful indicator of HI insult.
- Likelihood of sequelae after HI insult without a neonatal syndrome is not known.
- Specific Aspects –*Severity, duration and presence of seizures.*

Predictors of outcome: *Severity of Encephalopathy.*

- Finer et al. -using Sarnat and Sarnat staging
- 226 term asphyxiated babies ,173 and 145 examined at 3.5 and 8 yrs.
- Mild -No mortality and no neuro morbidity,
Severe –High mortality and morbidity among survivors.
- Moderate-most survived,20% had major disability BUT 35% of those with no disability had failure to achieve full academic potential in grade school.

Predictors of outcome: Duration of Encephalopathy

- >7 days stage 2 – bad prognosis.
- Finer et al (1985) ,Sarnat & Sarnat (1976) in 2 large series reported normal out come in infants with normal exam at 1 week or at discharge.
- These Outcomes did NOT include any learning disabilities.

Predictors of outcome: Seizures

- Seizures increase the risk of neurological sequelae by 2-5 fold.
- Seizures recalcitrant to treatment are uniformly associated with bad outcome.
- Early onset of seizure <4 hrs. has high risk of adverse outcome up to 75%.

EEG

- **Normal Outcome:**
 - *Mild Depression(or less) on day 1.*
 - *Normal background by day 7.*
- **Poor Outcome:**
 - *Burst suppression/Isoelectric tracing on any day.*
 - *Mild (or greater) depression after day 12.*

Neuroimaging

- CT
- US
- MRI

- MR spectroscopy
- Measurement of cerebral blood flow, velocity, or volume.

References

- *Fanaroff AA, Martin. Neonatal-Perinatal Medicine, Seventh edition*
- *Volpe JJ. Hypoxic-Ischemic encephalopathy .In: Volpe JJ; Neurology of the newborn; fourth edition.*
- *M V Johnston, Wako Nakajima: Neurobiology of Hypoxic Ischemic injury in the developing brain: Review ; Pediatric research, vol. 49, No. 6, 2001: 735-741.*
- *SR Leuthner, Low Apgar scores and definition of birth asphaxia: Ped. clinics of North America; vol. 51. No. 3, June 2004.*

Questions

- Define the AAP/ACOG criteria for diagnosing Birth asphaxia.?
- Enumerate the various organ systems that can be affected by asphaxia?
- List the investigations you should do on a baby with asphaxia?
- What is the name of the staging system used to quantify the severity of the encephalopathy?