Hipoxic ischemic encephalopathy

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Perinatal asphyxia

1. Definition

- **Perinatal asphyxia** - more appropriately known as hypoxic – ischemic encephalopathy – is characterized by clinical and laboratory evidence of **acute brain injury due to asphyxia**

- The primary causes of this condition are systemic hypoxemia and/or reduced cerebral blood flow (CBF)
Perinatal asphyxia

Fetal response to asphyxia illustrating the initial redistribution of blood flow to vital organs. With prolonged asphyxial insult and failure of compensatory mechanisms, cerebral blood flow falls, leading to ischemic brain injury.
Neonatal encephalopathy - clinical signs

- Disturbance in neurologic function, demonstrated by:
  - Difficulty in maintaining respirations
  - Hypotonia
  - Altered level of consciousness
  - Depressed or absent primitive reflexes, seizures, poor feeding
Diagnosis (AAP, ACOG)
all of the following must be present for the designation of perinatal asphyxia severe enough to result in neurologic injury

- Profound metabolic or mixed acidemia (pH < 7 in an umbilical artery blood sample, if obtained)
- Persistance of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurologic sequele (seizures, coma, hypotonia)
- Multiple organ involvements (kidneys, lungs, liver, heart, intestines)
- Lab studies
- Imaging studies
- Additional studies
Etiology

- Etiology multifactorial – but typically results from a serious hypoxic-ischemic event occurring before or during labor or at delivery,

- Maternal problems- hypotension, preeclampsia, chronic vascular disease

- Primary placental perfusion problems (true knot, abruptio placenta, uterine rupture)

- Fetal oxygenation/perfusion problems (fetomaternal hemorrhage, fetal thrombosis)

(Also the important role of the placental analysis (chronic villitis, chorioamnionitis)
Knotted cord

Prolapsed cord

Nuchal cord

Placental abruption
Treatment

- Hypothermia should be induced as early as possible to achieve maximum neuroprotection and edema blocking effect.

- The terapheutic hypothermia must be started within 6 hours from birth.
Global ischemic events may cause **decreased perfusion** and **injury** to vulnerable watershed regions of the developing brain.

Poor perfusion leads to lack of **oxygen** and **glucose**, resulting in Energy failure and loss of mitochondrial function, which is the central cellular problem underlying HIE.
In fetuses and newborns suffering from acute asphyxia after the adjustments fail, the **CBF can become pressure passive**, at which time the brain perfusion depends on systemic BP, which leads to brain injury secondary to diminished blood supply and a lack of sufficient oxygen. This leads to intracellular energy failure.

**Background pathophysiology**

- CBF falls below critical levels
- Energy failure

**Interventions NEED TO BE WITHIN 6 hrs of insult**
Background - pathophysiology

Without sufficient oxygen and glucose, adenosine triphosphate (ATP) production diminishes and energy-dependent membrane pumps fail, resulting in neurotransmitter release (glutamate), induction of destructive enzymes and free radical damage.
Background - patophysiology

Excitotoxic glutamate receptor-mediated injury can occur through overactivation of NMDA receptors, intracellular calcium accumulation—which triggers apoptosis.

Activation of AMPA receptors may result in necrotic death of mature oligodendrocytes.
If the newborn is resuscitated after a hypoxic–ischemic event, brain tissue reperfusion occurs, which may propagate a series of cellular events that evolve rapidly through reactive oxygen species, cytokines, and caspases—inducing cell dysfunction and death.
HIE – pathophysiology – delayed phase of neuronal injury

Following the initial phase of Energy failure from the injury, cerebral metabolism may recover following reperfusion, only to deteriorate in a secondary Energy failure phase.

It starts 6-24 hrs after and is characterized by mitochondrial dysfunction and initiation of the apoptotic cascade.
Background-pathophysiology

At the cellular level, neuronal injury is an evolving process.

The magnitude of the final neuronal damage depends on the duration and severity of the initial insult, combined with the effects of reperfusion injury, and apoptosis.

At the biochemical level, a large cascade of events follow HIE.

Potential pathways for brain injury after hypoxia-ischemia.
HIE – pathophysiology

The pattern of injury seen after hypoxia – ischemia can be largely explained by the excitatory circuit at this age (putamen, thalamus).

Finally, developing oligodendroglia is uniquely susceptible to hypoxia-ischemia. This white matter injury may be the basis for the disruption of long-term learning and memory faculties in infants with hypoxic-ischemic encephalopathy.
HIE – pathophysiology
• Birth histories consistent with HIE include description of intrauterine stress (fetal heart rate tracing abnormalities, meconium passage, history of difficult labour and delivery)

• Newborn with HIE typically have respiratory failure requiring positive pressure ventilation, may develop cardiac arrest,

• Low Apgar scores (< 5) at 5 min and 10 min of life

• pH of fetal umbilical artery less than 7.0; or base deficit greater than or equal to 12-15 mmol/l; or both
Clinical signs and symptoms

The clinical presentation of affected neonates may evolve over a period of 72 hrs, and is often categorized using sarnat staging:

- Mild encephalopathy
- Moderate encephalopathy
- Severe encephalopathy

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<tr>
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<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
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<tbody>
<tr>
<td>Consciousness</td>
<td>Hyperalert</td>
<td>Lethargic of obtunded</td>
<td>Stupor or coma</td>
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<td>Activity</td>
<td>Normal</td>
<td>Decreased</td>
<td>Absent</td>
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<tr>
<td>Neuromuscular control</td>
<td>Normal</td>
<td>Mild distal flexion</td>
<td>Mild hypotonia</td>
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<tr>
<td>Muscle tone</td>
<td></td>
<td>Overactive</td>
<td>Strong distal flexion</td>
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<td>Posture</td>
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<td>Strec reflexes</td>
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<td>Primitve reflexes</td>
<td>Suck</td>
<td>Weak</td>
<td>Weak or absent</td>
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<tr>
<td>Suck</td>
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<td>Weak, incomplete</td>
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<tr>
<td>Moro</td>
<td>Slight</td>
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<tr>
<td>Autonomic function</td>
<td>Pupil</td>
<td>Normal</td>
<td>Miosis</td>
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<tr>
<td>Pupil</td>
<td></td>
<td>Tachycardia</td>
<td>Bradycardia</td>
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<td>Heart rate</td>
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<tr>
<td>Seizures</td>
<td>None</td>
<td>Common</td>
<td>Uncommon</td>
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Stage 0 = Normal
Diagnosis

HIE is the most common cause of seizures in the neonatal period.

Seizures may be noted in the first 24 hours after birth.

Apneic events and vital sign instability may also be presentation of seizure activity.
Diagnosis

Serial examinations and monitoring are important to assess neonates with HIE since the clinical signs and symptoms often evolve over time.

Neonates with mild HIE may develop a normal examination by 12 hours of age, whereas neonates with more severe HIE remain stuporous, often with respiratory failure and dilated pupils that are fixed and poorly reactive to light.

In general, neonates who have a quick clinical recovery and a normal examination a 1 week of age typically have normal long-term outcomes.
Laboratory and ancillary studies

- Multisystem organ failure is common, evidenced by metabolic and hematologic abnormalities, hepatic, renal gastrointestinal and cardiac dysfunction
  
- Basic metabolic panel and an arterial blood should be obtained shortly after delivery

- Complete blood count
- Coagulation studies
- Liver function labs
- Creatinine
Neuroimaging

Cranial ultrasonography (US) can be used as a first line imaging tool in newborns with HIE.

Subtle signs of HIE may be difficult to detect with US.

In Severe HIE – US may demonstrate increased focal or diffuse brain parenchyma echogenicity, slit like ventricles, obliteration of extracerebral CSF.
Neuroimaging

MRI is the study of choice for neonates with HIE.

MRI performed in the newborn period has a high predictive value in neonates.
Management

- Initial steps should focus on promoting adequate oxygenation, ventilation, circulation.
- Serial monitoring of laboratory tests (blood gas basic metabolic panel, ionized calcium, lactate, CBC, liver enzymes, coagulation studies)
- Correction of metabolic derangements (hypoglycemia, hyperglycemia, hypocalcemia)
- Assessment of clinical and electrographic seizure activity
- Inotropic agents may be useful for hypotension
- Close monitoring of renal function/electrolytes
Management

TH (therapeutic hypothermia) 72 hours of cooling to 33.5 +/- 0.5°C followed by slow rewarming, 0.5°C per hour to normothermia is now the standard of care to treat neonates with moderate to severe HIE.

The benefit of TH for improving outcomes of newborns with HIE was investigated in numerous studies.
TH – complications

- Arrythmias – bradycardia, ventricular tachycardia
- Persistent acidosis
- Bleeding
- Subcutaneous fat necrosis
- Death
• less death and better neurodevelopmental outcomes for survivors
• TH has not been associated with a significant increase in the rates of major cardiac arrhythmia and hypotension or in the need for inotropic agents
• It appears that TH increases survival without increasing the rates of major disability, an IQ score below 70, or cerebral palsy in surviving children