Perinatal Asphyxia
tshinik hilo
dr' gisla sirotah
makhlet tinokot ogina, bi-t-holim ma'ar
16.11.16
Neonatal encephalopathy (NE) - a disturbance of neurologic function evident in the first days after birth in a newborn.

Characterized by a subnormal level of consciousness and depressed tone and reflexes, with or without seizures and often with impaired respiration and feeding abilities.

Intrapartum-related hypoxic events (“birth asphyxia”) may result in neonatal encephalopathy (NE).

NE is a broader term denoting a syndrome of neurologic disturbance owing to an intrapartum hypoxic insult or other causes (metabolic, genetic, infection, etc).
**Definitions**

- **Hypoxic Ischemic Encephalopathy (HIE)** specifically refers to encephalopathy associated with intrapartum injury from hypoxia and/or ischemia.

- **Hypoxia** = Diminished oxygen supply to tissue

- **Ischemia** = Diminished blood flow to tissue or organ

- **Asphyxia** = Disturbance of gas exchange in fetal-maternal circulation resulting in increased pCO2 and decreased pO2

- Brain hypoxia and ischemia due to systemic hypoxemia / reduced cerebral blood flow (CBF) or both - the primary physiological processes that lead to hypoxic-ischemic encephalopathy.
The initial compensatory adjustment to an asphyxial event is an increase in CBF due to hypoxia and hypercapnia.

Accompanied by a redistribution of cardiac output to essential organs (brain, heart and adrenal glands).

Blood pressure (BP) increase due to increased release of epinephrine further enhances this compensatory response.

If the hypoxic ischemic insult persists → failure of the early compensatory adjustments → CBF falls below critical levels → brain injury secondary to diminished blood supply and a lack of sufficient oxygen occurs.
Hypoxic Ischemic Encephalopathy

- Incidence of 1 to 4 per 1000 live births in the western world, and far more common in developing countries.

- The chance of irreversible damage or death following perinatal asphyxia is high, up to 65%.

- The severity of HIE can be defined as mild, moderate, or severe depending on clinical findings as described by Sarnat and Sarnat.
# Hypoxic-Ischemic Encephalopathy in Term Infants
## Sarnat and Sarnat Staging

<table>
<thead>
<tr>
<th>Signs</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
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<td>Good</td>
<td>Variable</td>
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AAP and ACOG guidelines for (HIE) indicate that all of the following must be present:

- Profound metabolic or mixed acidemia (**pH < 7**) in an umbilical artery blood sample, if obtained
- Persistence of an Apgar score of **0-3** for longer than 5 minutes
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia)
- Multiple organ involvement (eg, kidney, lungs, liver, heart, intestines)
Causes of Fetal Hypoxic-Ischemic Insult

**Maternal**
- Cardiac arrest
- Asphyxiation
- Severe anaphylactoid reaction
- Status epilepticus
- Hypovolemic shock

**Fetal**
- Fetomaternal hemorrhage
- Twin-to-twin transfusion syndrome
- Severe isoimmune hemolytic disease
- Cardiac arrhythmia

**Uteroplacental**
- Placental abruption
- Cord prolapse
- Uterine rupture
- Hyperstimulation with oxytocic agents
Hypoxic-ischemic injury may occur at any time during pregnancy, the birth process, or the neonatal period.

- 20% - Antepartum
- 35% - Intrapartum
- 35% - Antepartum + Intrapartum
- 10% - Post partum

The pattern of brain damage depends on the type and duration of the insult and the gestational age of the fetus / child at the time of the insult.
An acute hypoxic-ischemic insult leads to events that can be broadly categorized as **early (primary)** and **delayed (secondary)** neuronal death.

**Early or primary neuronal damage** = neuronal death of the necrotic type.

Recovery and reperfusion as occur with resuscitation fuel the pathways to **late (secondary) neuronal damage** through a relatively large number of pathophysiologic mechanisms that lead to apoptosis.

Starts within 6 to 8 hours after the primary insult.
Cellular Energy Failure

- Poor perfusion → rapid depletion of ATP, our cellular gasoline.

- Krebs cycle:  
  \[ \text{Glucose} + \text{oxygen} = 36 \text{ ATP} \]  
  \[ \text{Glucose without } \text{O2} = 2 \text{ ATP} + \text{lactic acid} \]

- ATP – needed for synthesis, transport, ion pumps
  - Sodium (Na), calcium (Ca) constantly leak into the cell
  - Potassium (K) constantly leaks out of cell
  - Ion pumps use ATP to pump Na & Ca out of cell, K into cell
  - No pump: Water follows Na into cell, cell swells and bursts

- No ATP → cell death
Necrosis vs. Apoptosis

Two types of cell death:

- **Necrosis** (early cell death): ATP-dependent Na+/K+ pumps fail, Na then H₂O influx, cell swelling, membrane fragmentation, inflammation
  - Neuron is destroyed.
  - Post-event cooling **not** helpful.

- **Apoptosis** (delayed cell death): membrane depolarization, glutamate release, calcium influx, cell shrinks, no inflammation
  - Cascade of Apoptosis: Starts 2-6 hrs after event.
  - Window of opportunity for body cooling therapy.
Mechanisms of ischemic brain injury

Hypoxia-ischemia

Primary neuronal death → Cytotoxic mechanisms → Delayed neuronal death

1 hour → 6 hours → Days

Modified from Gunn and Thoresen, 2006
INSULT

Therapeutic Window: Hypothermia Other

Primary energy failure (Minutes)
- Na⁺ overload
- Excitotoxicity

Reperfusion

Cerebral metabolism transiently recovers
- Ca²⁺ overload
- ROS, NO

Secondary phase (Hours to days)
Between 6-72 h after insult
- Mitochondrial dysfunction
- Caspases activation

Hypoxic ischemic brain injury

Interventions NEED TO BE WITHIN 6 hrs of insult

Immediate necrotic cell death

Delayed apoptotic cell death
Assessment tools

- Physical examination

The Sarnat classification is based on clinical and EEG findings 24 hours after the insult.

It has been modified to be used shortly after the insult for selecting neonates to determine eligibility for therapeutic hypothermia.

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Clinical findings

- **Mild HIE:**
  - Mild hypertonia (increased tone)
  - Brisk deep tendon reflexes
  - Irritable, high-pitched cry
  - Poor feeding, sloppy, disorganized
  - CNS examination normal by day 3-4

- **Moderate HIE:**
  - Marked hypotonia and lethargy
  - Pausing or mild apnea
  - May have onset of seizures in 1st 24 hrs
  - Full recovery within 1-2 weeks possible
  - Quicker recovery → better long-term outcome
Clinical findings

- **Severe HIE:**
  - Minimal / no response to stimulus
  - No gag reflex
  - Pupils fixed / dilated
  - Stuporous or comatose / floppy
  - Irregular breathing / apnea $\rightarrow$ ventilator support
  - Early seizures but often EEG goes flat

- **Survivors of Severe HIE:**
  - Level of alertness improves by day 4-5
  - Spontaneous respiration by day 4-5
  - Hypotonia / feeding difficulties **persist**
  - Gastrostomy +/- fundoplication often needed
Systemic complications of HIE

- **Pulmonary:**
  - Meconium Aspiration Syndrome
  - Persistent Pulmonary Hypertension

- **Renal:**
  - Oliguria
  - Acute Renal Failure

- **Metabolic:**
  - Hypoglycemia
  - Hyponatremia
  - Hypocalcemia

- **Gastrointestinal:**
  - Motility Disorders
  - Necrotizing Enterocolitis
  - Elevated Liver Enzymes

- **Hematologic:**
  - Coagulation impairment
  - DIC

- **Cardiac:**
  - Impaired Cardiac Contractility
  - Myocardial Infarction

- **Adrenal Hemorrhage**
Assessment tools

- **EEG** – 16-channel

- Normal traces almost invariably predict a normal outcome, whereas persistent, severely abnormal traces predict an adverse outcome

- **Amplitude-integrated EEG (aEEG)**

  - 1-2 channels
  - Bedside
  - Continuous monitoring of brain activity.
  - Easy around-the-clock access and easy interpretation based on pattern recognition.
### Amlitude integrated EEG (aEEG)

<table>
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<tr>
<th>Voltage classification</th>
<th>aEEG trace 6cm/hour</th>
<th>Pattern classification</th>
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<tr>
<td>Normal Trace</td>
<td><img src="image" alt="Normal Trace Graph" /></td>
<td>CNV, Continuous Normal Voltage</td>
</tr>
<tr>
<td>Normal</td>
<td><img src="image" alt="Normal Graph" /></td>
<td>DNV, Discontinuous Normal Voltage</td>
</tr>
<tr>
<td>Moderately abnormal</td>
<td><img src="image" alt="Moderately Abnormal Graph" /></td>
<td>BS, Burst Suppression</td>
</tr>
<tr>
<td>Abnormal</td>
<td><img src="image" alt="Abnormal Graph" /></td>
<td>LV, Low Voltage, FT, Flat Trace (isoelectric)</td>
</tr>
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</table>

- **Normal Trace**: Lower margin >5μV, upper margin >10μV
- **Moderately abnormal Trace**: Lower margin ≤5μV, upper margin >10μV
- **Abnormal Trace**: Lower margin <5μV, upper margin <10μV
The exact nature of the injury depends on the severity of hypotension and hypoxia.

In term infants – injury in **watershed-border zones**; namely parasagittal grey matter and subcortical white matter.

Profound HIE in term babies results in **thalami and basal ganglia** as well as **sensorimotor cortex** (perirolandic region) injury.
Neuroimaging

- **Ultrasonography:**
  - Sensitive for the detection of hemorrhage, PVL and hydrocephalus.
  - Not the best in assessing abnormalities related to HIE.
  - Can be helpful when performed sequentially during the first week of life.
  - In severe cases, the ventricles are difficult to visualize owing to edema and are referred to as slitlike.
  - Changes in the thalami and basal ganglia may be subtle, but usually become clearer by the end of the first week of life.
  - Echogenicity in the white develops gradually over a period of days.
  - Severe HIE results in decreased Resistive index (RI).

- **CT:**
  - The least sensitive modality for evaluation of HIE.
MRI:
The most sensitive and specific imaging technique for examining infants with suspected hypoxic-ischemic brain injury.

Help exclude other causes of encephalopathy such as hemorrhage, cerebral infarction, neoplasms, or congenital malformations.

Is able to show different patterns of injury - abnormalities in the thalami and basal ganglia and injury to the watershed cortical regions.

Best when done during the second half of the first week.
Cortical Injury

Basal Ganglia Injury
The diving reflex occurs during asphyxia to maintain blood flow to vital organs (brain) at the expense of less-vital organs.

This is the basis of systemic complications after a significant hypoxic-ischemic insult - the heart, kidneys, and liver are the most vulnerable organs.

Resuscitation

- **Cardiovascular:** Maintain normal BP
- **Metabolic:** Avoid hypoglycemia and hyperglycemia
- **Treat seizures:** Prevent additional damage
HIE – Medical Care

- **Ventilation:** Keep carbon dioxide level normal (40-50 mmHg)
- **Avoid Hyperoxia:** 100% oxygen toxic
- **Hematologic:** Treat thrombocytopenia, DIC

- In past, no effective treatment.
- **Now → Therapeutic Hypothermia**
HIE – Therapeutic Hypothermia

Mechanisms:
- Reduces metabolic rate (7-8% lower / 1°C)
- Reduces ion flux (calcium, sodium)
- Decreases excitatory transmitter release
- Reduces vascular permeability and edema
- Reduces apoptosis

Types:
- Whole body vs. Selective head cooling

Timing:
- Up to 6 hrs of injury
- Maintain cooling for 72 hrs
- Re-warm over 6-8 hours
מתווכ: הנחייה קLINית של האיגוד הישראלי לאנוטולוגיה

נושא: טיפול ביילודים, שסובלים מאנצפלופתיה היפוקסית איסכמית באמצעות היפותרמיה בינונית

גיל הרוי של לוחות 36 שבועות

تانאים מוקדמים (דרישת תנאים אחה ללוחות)

1. אין אפגר של 5 או נומר ממוצע, בגיווי 10 דקות.
2. החיה, שgormבשה מעל 10 דקותוכלび להחלולה ללוחות פעולתם במנוחה אםInvocation.
3. המטרに戻ובטיות בעורר PH ממוצע של 0.7 Asher NMD BED 16 טורבורי (עורק, וריד).
4. תוספס של 16 maybe ללייט או יוצר בד טבוריאו בד מינתון עד גיל

שעיה.
ב/context ש crédit ההכרה המוקדמים לעיל,DER לקוים של ההנאים הבアイים:

1. שינוי מהמצב ההכרה (לטרגיות, סטטור ואו חוסר הכרה)

2. התמקדות ת سياسي אחד מתוך המהנאים הבアイים:

   - היופוטוני
   - פעיעה בשחרים, כלל פגייעה באישיות ובהתנועה העיניים
   - הזר מציינת חולש או של ימין ל흑ה
   - פרוכוסים קליים

3. טור מגלו 12 שעון המילדה (יש לשאוף לתחנת טיופולות 6 שעון).
Therapeutic Hypothermia

- Since the reports in 2005 of two randomized controlled trials (RCTs) in full-term neonates with perinatal asphyxia, hypothermia has become standard of care for babies in whom perinatal asphyxia is followed by encephalopathy.

- The primary outcome in the RCTs was death or disability at 18 months.

<table>
<thead>
<tr>
<th>Table 5. Stage of Hypoxic-Ischemic Encephalopathy (HIE) and Response to Therapeutic Hypothermia</th>
</tr>
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<tbody>
<tr>
<td>Moderate HIE</td>
</tr>
<tr>
<td>Whole body cooled NICHD trial (Shankaran et al, 2005) (39)</td>
</tr>
<tr>
<td>Cool Cap trial (Wyatt et al, 2007) (41)</td>
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Therapeutic Hypothermia

- Despite the differences between the RCTs, the outcome at 18 months shows improved survival without neurologic abnormality and significantly reduced cumulative outcome of death and severe disability.

- Neuroprotection is better in neonates with moderate compared to severe encephalopathy.

- Number to benefit is approximately 7.

- No differences have been demonstrated between head cooling or whole body hypothermia.
Therapeutic Hypothermia

- Complications of hypothermia:
  1. More common - Sinus bradycardia and thrombocytopenia
  2. Uncommon - Increased pulmonary hypertension and subcutaneous fat necrosis
Selective head cooling

Early studies show that reducing a baby’s head temperature by a few degrees can reduce damage to the brain after certain types of brain damage.
Whole body cooling
Future neuroprotective strategies

- At present, clinical trials are being performed examining the neuroprotection by different interventions in addition to hypothermia.

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Interventions</th>
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<tbody>
<tr>
<td>↓ cerebral metabolic rate</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Block NMDA receptor channel</td>
<td>Magnesium</td>
</tr>
<tr>
<td>↓ glutamate release</td>
<td>Adenosine, Adenosine agonists, Adenosine uptake inhibitors</td>
</tr>
<tr>
<td>Inhibit voltage-sensitive Ca++ channels</td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>↓ free radical reactions</td>
<td>Free radical scavengers, Allopurinol, Vitamin C, E, Super oxide dismutase (SOD)</td>
</tr>
<tr>
<td>Prevent free radical formation</td>
<td>Indomethacin, Iron chelators, Allopurinol, NOS inhibitors</td>
</tr>
<tr>
<td>↓ inflammatory response</td>
<td>Allopurinol, Inflammatory antagonists (blocking IL-1 and TNF-α, steroids)</td>
</tr>
<tr>
<td>Attenuate apoptosis pathway</td>
<td>Caspase inhibitors</td>
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</tbody>
</table>
Future neuroprotective strategies

- **Ongoing intervention trials:**
  - **Allopurinol**: Free radical scavenger
  - **Xenon**: NMDA antagonist, less apoptosis
  - **Erythropoietin**: ↑ vasculogenesis / neurogenesis, ↓ inflammation, ↓ oxidant damage, ↓ apoptosis
  - **Stem Cell Infusion**: (umbilical cord blood) migrate to damage area → helps repair.
Outcome of HIE

Severe HIE:
50-75% - mortality by 1 month
80% survivors - significant mental retardation, cerebral palsy, seizures

Moderate HIE:
30-50% - significant long term problems
10-20% - minor neurologic abnormalities

Mild HIE:
Most escape long-term complications
Outcome of HIE

- The risk of cerebral palsy related to HIE – \textbf{5-10\%}.
- \textbf{2/1000} live births in the general population.

- Only in 3-10\% of children with CP – signs of perinatal asphyxia.

- Most cases are \textbf{not} related to a perinatal event.

- \textbf{Spastic quadriplegia and ataxic CP}. 

\textit{CP: Spastic Quadriplegia}

- “Fisting”
- “Scissoring” of lower limbs
Predictors of Mortality and Neurologic Morbidity after Perinatal Hypoxic-Ischemic Insult

- Extended very low Apgar scores
- Long time to establish spontaneous respiration
- Prolonged abnormal neonatal neurologic examination:
  - Abnormal brain imaging using ultrasonography and magnetic resonance imaging
  - Abnormal electrophysiology: suppressed EEG or amplitude-integrated EEG background pattern, status epilepticus; abnormal evoked potentials (visual, brainstem auditory, and somatosensory)
Prevention

- The use of intrapartum markers such as fetal heart rate monitoring are poor predictors of neonatal outcomes and long-term risk of cerebral palsy.

- With the exception of hypothermia therapy, no other therapy has consistently shown efficacy in human infants.
THANK YOU FOR listening TO MY PRESENTATION