Neonatal Asphyxia

Raja Nandyal, MD; FAAP;
Neonatal Section- Department of Pediatrics
OUHSC
June 27th 2013
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Speaker Disclosure

- I have no financial relationships or affiliations to disclose.
- I am a full time faculty member of Oklahoma University Health Sciences center (the department of Pediatrics) and Oklahoma University Children’s Physicians group.
- There is no reference to off-label or investigational use of drugs or products in my presentation.
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What is Perinatal Asphyxia?

- Perinatal asphyxia, results from an **inadequate intake of oxygen** by the baby during the birth process – before, during, or just after birth.

- **Decreased oxygen intake** can result in **chemical changes** in the baby's body that include **low levels of oxygen** (hypoxemia) in the blood, and **too much of acid build up** (acidosis) in the blood.
• Perinatal asphyxia results from compromised placental or pulmonary (lung) gas exchange.

• This compromise can lead to lack of O2 (hypoxia) and increased CO2 (hypercarbia) in the blood.

• Prolonged and severe lack of oxygen (hypoxia) → breakdown of glucose or conversion of glucose in the absence of O2 (anerobic glycolysis) → lactic acid production, first in muscle and heart and then in the brain.

• Lack of sufficient blood flow (ischemia) to all or a part of an organ can be both a cause and a result of hypoxia.
• Hypoxia and acidosis can depress heart muscle (myocardial) function → low BP (hypotension) and lack of sufficient blood flow (ischemia)

• **Ischemia** (lack of sufficient blood flow) → decreased oxygen delivery → can further compromise, and disrupt delivery of substrate and removal of metabolic and respiratory by-products (eg, lactic acid, carbon dioxide).
- Decreased Circulation (placenta or infant) →

- **Decreased O2 levels** and **increased CO2 levels** in the blood of the infant →

- **Production of lactic acid** →

- Decreases heart’s pumping power →

- Low BP and **decreased blood flow** → to various organs (Brain, heart and adrenals affected late)
- **Signs and symptoms** of Neonatal asphyxia may not be very obvious, but the most common S/S include:

- **Before birth**, abnormal fetal heart rate and low pH levels, indicating too much acid

- **At birth**, poor skin color, low heart rate, weak muscle tone, gasping or weak breathing, and meconium stained amniotic fluid
All organs can be affected by perinatal asphyxia.

- So, S/S of involvement of various organs may be there.

- **HIE** (Hypoxic Ischemic Encephalopathy) is the most widely studied, as it has the most serious sequelae.
Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants

Seetha Shankaran,
Eunice Woldt,
Thomas Koepke,
Mary P. Bedard,
Raja Nandyal

Department of Pediatrics, Wayne State University School of Medicine, and Children's Hospital of Michigan, Detroit, MI U.S.A.
The multisystem effects of Asphyxia

- GA: Mean GA 40 ± 1 (mean ± S.D); Weight: 3434 ± (mean ± S.D)
- Total: 28 (all AGA); 4 babies died (<5 days)
- Lungs: 20
- Brain: 19
- Kidneys: 13
- Heart: 12
- Metabolic: 12
- Blood: 9
What is HIE? Why are we concerned?

- Neonatal asphyxia causes hypoxic–ischemic encephalopathy, (HIE), an involvement of brain from low oxygen and low blood flow → results in a poor neurological prognosis

- **HIE**: Incidence: One per 1000 live births (USA)

- 25% of infants with HIE die in the neonatal period

- 33 to 50% of survivors- permanent neurodevelopmental disabilities (CP, MR)
• **A syndrome** is the association of several clinically recognizable features, signs and symptoms in an infant.

• **Neonatal encephalopathy** is a heterogeneous and multifactorial syndrome characterized by signs of **central nervous system (CNS) dysfunction** in newborn infants.

• Clinical suspicion of neonatal encephalopathy should be considered in any infant exhibiting an *abnormal level of consciousness, seizures, tone and reflex abnormalities, apnea, aspiration, feeding difficulties, and an abnormal hearing screen.*
"Neonatal encephalopathy" has emerged as the preferred term to describe CNS dysfunction in the newborn period.

While neonatal encephalopathy was once automatically thought to be because of lack of oxygen and sufficient blood flow (hypoxia-ischemia), it is now known that hypoxia-ischemia is only one of many possible contributors to neonatal encephalopathy.

Whether a particular newborn's encephalopathy is from hypoxic-ischemic brain injury is often unclear.
• **Neonatal encephalopathy and Cerebral Palsy:**
  Executive summary.

• American College of Obstetricians and Gynecologists (ACOG)


• **ACOG Committee Opinion. Number 326, December 2005.**
  Inappropriate use of the terms fetal distress and birth asphyxia.

• Committee on Obstetric Practice, American College of Obstetricians and Gynecologists


• **We DO NOT USE the Word “Birth Asphyxia”**
Criteria for acute intra-partum events sufficient to cause cerebral palsy

All four criteria must be met:

Evidence of metabolic acidosis: umbilical artery pH < 7 and base deficit ≥ 12 mmol/L at delivery

Early onset of severe or moderate neonatal encephalopathy in infants ≥ 34 weeks of gestation

Cerebral palsy of the spastic quadriplegic or dyskinetic type

Exclusion of other identifiable etiologies (eg, trauma, coagulation disorders, infection, genetic disorders)

Criteria that suggest an intra-partum timing of an event that may be related to the development of cerebral palsy but is not specifically asphyxia

A sentinel hypoxic event occurring immediately before or during labor

A sudden and sustained fetal bradycardia or absence of fetal heart rate variability in the presence of persistent late or variable decelerations.

This usually occurs after a hypoxic sentinel event with a normal fetal heart rate pattern prior to the event.

Apgar score of 0 to 3 after five minutes

Onset of multisystem involvement within 72 hours of birth

Early imaging studies showing evidence of an acute nonfocal cerebral abnormality

Management:

- **Prevention**: Anticipation (based on risk factors); Preparation; Coordination; Communication with the family

- **Team Approach**:
  - Neonatal Resuscitation Program (**NRP**) - USA
  - *Helping Babies Breath* (developing countries)
Management:

- Hold Feeds until we make sure that the infant is stable
- IV Fluids - Fluid restriction (to avoid potential complications)
- Blood tests - CBC, metabolic panel, blood gases, blood culture etc
- Other tests:
  - CXR, Echo, Brain monitor (CFM), EEG, CT/MRI etc
- Brain monitor (CFM)
Management:

- Correction of Hypoglycemia, hypocalcemia etc
- Control of Seizures - Anticonvulsants
- Control of Blood pressure (Vasopressors/Inotropes)
- Renal management - Dopamine (low dose - not evidence based)
- **Therapeutic hypothermia**
Until recently, there are no therapies other than supportive measures for perinatal HIE, a condition associated with high neonatal mortality rates and severe long term neurologic morbidity.

Although hypothermia was used for “asphyxia neonatorum” in 1955, only in the past decade have systematic studies been carried out to address the safety and efficacy of this therapy in HIE.
Therapeutic Hypothermia

- Two types:
  - Head Cooling
  - Total Body Cooling
The Six Hour Clocks of Italy

- Apparently common between the 15th and 17th centuries, but very few survive.
- There is only one hand and the numerals go from one to six, dividing the day into four parts to regulate the monastic ‘hours’ of prayer.
Cooling Equipment
Term Infants (> 36 weeks- Head Cooling; >35 weeks Total body)

Admitted at < 6 hours of Age to NICU (with Birth Asphyxia, or Depression- Specific Criteria exist))

Brain hypothermia can be achieved safely using either selective head cooling with mild systemic hypothermia (temp 34°C to 35°C) or total body cooling (temp 33 to 34°C) for 72 hrs
At the cellular level, hypoxia-ischemia results in two phases of energy failure.

The **primary phase** follows the decrease in blood flow and oxygen supply with fall in ATP, failure of the Na+/K+ pump, depolarization of cells, lactic acidosis, release of excitatory amino acids, calcium entry into the cell and, if severe, cell necrosis.

Following resuscitation and reperfusion, there is a **latent period** with normalization of oxidative metabolism lasting *6 h to 12 h*, which is the therapeutic window for neuroprotective interventions.

*A Peliowski-Davidovich; Canadian Paediatric Society, Fetus and Newborn Committee Paediatr Child Health 2012;17(1):41-3*
At the cellular level, hypoxia-ischemia results in two phases of energy failure.

The **secondary phase** of energy failure develops at **12 h to 36 h**, and may last seven to 14 days with initiation of apoptosis, mitochondrial failure, cytotoxic edema, accumulation of excitatory amino acids and release of free radicals terminating in cell death.

This **secondary phase** is associated with worsening of HIE and correlates with poor outcomes.

A Peliowski-Davidovich; Canadian Paediatric Society, Fetus and Newborn Committee Paediatr Child Health 2012;17(1):41-3
Head Cooling (Cool Cap)
• Selective head cooling with mild systemic hypothermia after neonatal encephalopathy:
  • a multicentre randomised trial.


THE COOL-CAP TRIAL

In this trial, 234 term infants with moderate to severe HIE were randomized to conventional care or selective head cooling (while maintaining core body temperature at 34-35°C) for 72 hours followed by rewarming to normothermia.
Systemic effects and their incidences in the control group during the hospital course included the following:

- Respiratory distress (78 percent)
- Abnormal renal function (70 percent)
- Elevated liver function studies (53 percent)
- Hypotension (52 percent)
- Hypocalcemia (43 percent)
- Prolonged coagulation times (42 percent), platelet count below 100,000/microL, coagulopathy (14 percent)
- Metabolic acidosis (23 percent)
- Hypoglycemia (17 percent)
Total Body Cooling
• Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy.


In this study, the incidence of systemic effects during the hospital course in the control group was lower than the previously discussed trial.

- Very low BP requiring meds (inotropes- 33 percent)
- Persistent pulmonary hypertension (22 percent)
- Decreased Urine output (22 percent) and no urine (4 percent)
- Liver dysfunction (15 percent)
- Hypoglycemia (15 percent) and hypocalcemia (19 percent)
- Disseminated intravascular coagulopathy (11 percent)
Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care.

Each systematic review addresses a clearly formulated question; for example: *Can antibiotics help in alleviating the symptoms of a sore throat?*

All the existing primary research on a topic that meets certain criteria is searched for and collated, and then assessed using stringent guidelines, to establish whether or not there is conclusive evidence about a specific treatment.

The reviews are updated regularly.
Therapeutic hypothermia for hypoxic ischemic encephalopathy

Therapeutic hypothermia may reduce mortality and major neurodevelopmental disability in neonates with hypoxic ischemic encephalopathy (level 2 [mid-level] evidence).

Systematic review of 11 randomized trials comparing therapeutic Hypothermia.
Levels of evidence for clinical application

Level 1 - formal, open, clinical randomised-controlled trials

Level 2 - case controlled trials (comparisons made but not randomised)

Level 3 - observational studies (including surveys and questionnaires)

Level 4 - anecdotal evidence (including independent user comments and reviews)

Level 5 - methodological verification and validation studies
Therapeutic hypothermia for hypoxic ischemic encephalopathy

Whole-body hypothermia evaluated in 6 trials

Selective head-cooling with mild systemic hypothermia evaluated in 5 trials

Initiated prior to six hours after birth vs. standard care in 1,505 term or late preterm neonates with moderate or severe encephalopathy and perinatal asphyxia
The Thai **six-hour clock** is a traditional time system used in Thailand and Laos. It splits the day into 4 parts.
Childhood Outcomes after Hypothermia for Neonatal Encephalopathy


This multi center study involved 208 infants with moderate or severe encephalopathy who were randomly assigned at less than 6 hours of age to undergo Total Body Cooling (102 infants) or usual care (106 infants).

The follow-up visits at 6 to 7 years of age were conducted between August 2006 and August 2010.

The median age at follow-up was 6.7 years in the hypothermia group and 6.8 years in the control group.
Among survivors at 6 to 7 years:

The rate of cerebral palsy: Hypothermia group → 17%
Control group → 29%

The rates of blindness were 1% and 4%

The rate of hearing impairment (requiring aids) → 5% & 2%

Whole-body hypothermia did reduce the rate of death and did not increase the rates of a low IQ score or severe disability among survivors.
Other Issues: Subacute Fat Necrosis
**Subcutaneous fat necrosis (SFN)** of the newborn presenting within a week of therapeutic hypothermia treatment for perinatal asphyxia.

SFN has been described following therapeutic hypothermia.

Neonatal fat is composed of saturated fatty acids (stearic and palmitic acids) with a relatively high ‘melting point’.

Exposure to a cold surface in susceptible infants may induce the fat to undergo crystallization, leading to necrosis.
X-ray of Infant with Meconium Aspiration Syndrome
F = frontal horn of lateral ventricle
3 = third ventricle
O = occipital horn of lateral ventricle
Hydrocephalus

Normal

Hydrocephalus

Ventricles

Brain

Spinal cord

Compressed brain tissue

Enlarged ventricles
Grade III IVH → Hydrocephalus
Figure 1. Non-contrast head CT demonstrates an acute hemorrhage in the right frontal lobe with associated vasogenic edema (blue arrow), and right-to-left midline shift (red arrowhead). The presence of sulcal effacement suggests diffuse cerebral edema.
Classification of Neonatal Seizures

- Clinical
- Electroencephalographic
Classification

I. Clinical Seizure

- Subtle
- Tonic
- Clonic
- Myoclonic
Seizures:

II. Electroencephalographic seizure

- Epileptic
- Non-epileptic
Reasons for neonatal seizures

**Acute Metabolic**

- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Hypo- or hypernatremia

**Withdrawal syndromes** associated with maternal drugs or medications

**Iatrogenic** associated with inadvertent fetal administration of local anesthetic

Rare **inborn errors of metabolism** (including pyridoxine responsive)
Cerebrovascular

Hypoxic ischemic encephalopathy

Arterial and venous ischemic stroke

Intra-cerebral hemorrhage

Intra-ventricular hemorrhage

Sub-dural hemorrhage

Sub-arachnoid hemorrhage

CNS infection

Bacterial meningitis

Viral meningoencephalitis

Intrauterine (“TORCH”) infections
Developmental

Multiple forms of cerebral dysgenesis

Other

Rare genetic syndromic disorders

Benign neonatal familial convulsions (sodium and potassium channel mutations identified)

Early myoclonic encephalopathy
Choice of anticonvulsants for preterm and term neonates:

Phenobarbital

Lorazepam (Ativan)

Phosphenytoin

Levetiracetam (Keppra)

Midazolam (Versed)

Topiramate

Lidocaine
All HIE Infants need to be followed for the Neurodevelopmental Outcome assessment $\rightarrow$ Sooner Start
“I want to turn the clock back to when people lived in small villages and took care of each other.” — Pink Ranger