Neonatal Encephalopathy: Case Studies

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Nothing to disclose.

Learning Objectives

- Recognize and evaluate encephalopathy in newborns
- Describe the utility of brain MRI and EEG for diagnosis and prognosis in neonatal encephalopathy
- Identify treatments available for neonatal encephalopathy
Outline

- Define neonatal encephalopathy and hypoxic-ischemic encephalopathy
- Clinical evaluation of encephalopathy
- Therapeutic hypothermia
- Neuromonitoring
- Neonatal seizures
- Neuroimaging
- Perinatal stroke

Background

- Injury to the developing brain is a major cause of death and neurologic disability worldwide
- For survivors
  - Cerebral Palsy
  - Intellectual disability
  - Epilepsy

Case 1

- Term male LGA infant
- Uncomplicated pregnancy
- Delivery via stat C/S for prolapsed cord
- Depressed at birth, HR undetectable, apneic
  - Apgar 1 at 1 min, 4 at 5 min, 6 at 10 min
- Resuscitation in delivery room
  - PPV, intubation, spontaneous respiratory effort at 19 minutes
- Laboratory results
  - Cord VBG pH 6.9, base deficit 14
Case 1

- Transfer to Children’s Hospital and Clinics - St. Paul NICU
- Initial neurologic exam
  - Bicycling movements concerning for seizures
  - Minimal spontaneous movement, decreased level of consciousness, hyperreflexia

Neonatal Encephalopathy

- Decreased level of consciousness
- Seizures
- Abnormal muscle tone or strength
- Abnormal reflexes
- Abnormal cranial nerves
- Feeding difficulties
- Respiratory insufficiency or apnea
- Irritability
- Autonomic dysfunction
- Encephalopathy

Evaluation of Neonatal Encephalopathy

- Clinical history
  - Pregnancy, delivery, gestational age, postnatal course, family history
- Neurologic exam including severity of encephalopathy
- Diagnostic studies
Causes of Encephalopathy in Newborns

- Hypoxic-ischemic insult (50-80%)
- Intracranial hemorrhage
- Perinatal stroke
- Traumatic brain injury
- Meningitis/encephalitis
- Congenital brain malformation
- Epileptic encephalopathies
- Inborn errors of metabolism
  - Hypoglycemia
  - Electrolyte imbalance
    - Hypocalcemia
  - Severe hyperbilirubinemia
  - Systemic illness (organ failure, sepsis)

Neonatal Hypoxic-Ischemic Encephalopathy

- Mechanism of injury
  - Interruption in blood flow or gas exchange to and from fetus
  - Hypoxic-ischemic injury
- Most common cause of acute neurologic impairment and seizures in term neonates
- 1-6 per 1000 live births in developed countries
- Cause of 1 in 5 neonatal deaths worldwide

Neonatal Hypoxic-Ischemic Encephalopathy

- Clinical features consistent with acute peripartum or intrapartum event
  - Apgar scores <5 at 5 and 10 minutes
  - Metabolic acidosis
    - Cord arterial pH <7.0 or base deficit ≥12 mmol/L
  - Brain MRI/MRS consistent with hypoxia-ischemia
  - Multisystem organ failure
Neonatal Hypoxic-Ischemic Encephalopathy

- Sentinel hypoxic or ischemic event immediately before or during labor and delivery
  - Ruptured uterus
  - Placental abruption
  - Umbilical cord prolapse
  - Amniotic fluid embolus with severe/prolonged maternal hypotension and hypoxemia
  - Maternal cardiovascular collapse
  - Maternal fetal hemorrhage
  - Fetal hemorrhage secondary to vasa previa

- Specific patterns in fetal heart trace can suggest hypoxic-ischemic event

Clinical Encephalopathy: Mild

- Increased muscle tone
- Deep tendon reflexes brisk
- Transient behavioral abnormalities
  - Poor feeding
  - Excessive crying, irritability
  - Excessive sleeping
- Normalize 3-4 days of life
Clinical Encephalopathy: Moderate

- Lethargic
- Low tone
- Depressed deep tendon reflexes
- Primitive reflexes sluggish or absent
- Apnea
- Seizures
- Possible full recovery 1-2 weeks
- Initially well or mild encephalopathy followed by sudden deterioration

Clinical Encephalopathy: Severe

- Stupor or coma
- Low tone
- Depressed deep tendon reflexes
- Irregular breathing
- Absent primitive reflexes
- Abnormal eye movements
- Pupils dilated, fixed or poorly reactive
- Early seizures
- Irregular HR and BP
- Increased alertness 4-5 days of life
- Persistent feeding and tone abnormalities

Modified Sarnat Scale

<table>
<thead>
<tr>
<th>Severity Stage</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Alert, hyperalert</td>
<td>Lethargic, obtunded</td>
<td>Stuporous</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Normal</td>
<td>Decreased</td>
<td>No activity</td>
</tr>
<tr>
<td>Posture</td>
<td>Normal</td>
<td>Distal flexion, full extension</td>
<td>Decerebration</td>
</tr>
<tr>
<td>Tone</td>
<td>Normal or hypertonia</td>
<td>Hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Normal</td>
<td>Exaggerated</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Normal</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Autonomic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>Normal</td>
<td>Constricted</td>
<td>Dilated/non-reactive</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Normal</td>
<td>Bradycardia</td>
<td>Variable HR</td>
</tr>
<tr>
<td>Respiration</td>
<td>Normal</td>
<td>Periodic breathing</td>
<td>Apnea</td>
</tr>
</tbody>
</table>
Case 1

- Intrapartum event: prolapsed cord
- Laboratory evidence of hypoxic-ischemic insult
  - Metabolic acidosis
- Clinical syndrome of neonatal encephalopathy
- Does the patient meet criteria for therapeutic hypothermia?

Therapeutic Hypothermia: Inclusion criteria

- ≥36 weeks gestation and birth weight > 1800 grams
- Hypothermia can be initiated <6 hrs of life
- Evidence of HIE or perinatal depression/asphyxia
- Laboratory criteria
  - Cord or infant blood gas within 1 hr of age
    - pH <7.00 OR base deficit ≥16 meq/L
  - OR blood gas with pH 7.01-7.15 or base deficit 10-15.9 AND Apgar ≤5 at 10 min or ventilation required for at least 10 min
- Neurologic exam
  - Moderate or severe encephalopathy based on modified Sarnat Score (Stage 2 or 3)
Therapeutic Hypothermia: Exclusion criteria

- Major congenital anomalies
- Chromosomal syndromes
- Major head trauma causing intracranial hemorrhage
- Condition not compatible with survival

Cochrane Review 2013: Cooling for newborns with hypoxic-ischemic encephalopathy

- 11 randomized controlled trials through May 2012
- 1505 term and late preterm infants
- Moderate/severe encephalopathy and evidence of peripartum asphyxia
- Cooling instituted <6 hours of age
- Outcome at 18 months
  - Statistically significant and clinically important
    - Reduction in death, RR 0.75, NNT 11 (11 studies, 1468 infants)
    - Reduction in neurodevelopmental disability of survivors, RR 0.77, NNT 8 (8 studies, 917 infants)
- Adverse effects of cooling minimal
- Benefits of cooling outweigh short-term adverse effects

Neuroprotective Mechanisms of Hypothermia

- Reduction in cerebral metabolism
  - Prevents edema and loss of membrane potential
  - Reduces accumulation of glutamate, lactate, nitric oxide
  - Inhibits platelet activating factor, inflammatory cascade
  - Inhibits excito-oxidative cascade leading to secondary energy failure
  - Inhibits enzymes responsible for apoptosis
  - Reduces extent of brain injury
  - Decrease in seizures???

Shankaran 2012, Johnston 2011
Case 1 Follow Up

- Whole body hypothermia for 72 hours
- EEG mild encephalopathy (discontinuous)
- Brain MRI normal
- Home on AED, tapered off outpatient
- Development and neurological exam at 12 months normal

Case 2

- Term AGA female infant delivered via uncomplicated repeat C/S following normal pregnancy
- Events at 7 hrs of life in well baby nursery
  - Stiffening with apnea followed by limpness and pallor
  - Brief, self-resolved
  - During feeding and during bath
- Labs: normal electrolytes, CRP, CBC
- Transferred to NICU for further evaluation

Case 2

- Spells recurred
- Clinical encephalopathy emerged
  - Feeding difficulties
  - Hypotonia
  - Decreased level of alertness
Diagnostic Studies for Neonatal Encephalopathy

- Neuromonitoring
  - aEEG
  - Conventional EEG - routine
  - Conventional EEG - prolonged video
- Laboratory studies
  - Blood
  - Urine
  - CSF
- Neuroimaging
  - Head Ultrasound
  - Head CT
  - Brain MRI

Neuromonitoring in the NICU

- Indications
  - Evaluate seizures
  - Differential diagnosis of paroxysmal events
  - Electrographic seizures in high risk infants
  - Assess risk for seizures
  - Monitor anticonvulsant therapy
  - Prognosis
    - Severity and duration of abnormalities predictive
  - Diagnostic evaluation of encephalopathy

Shellhaus et al. 2011

Neuromonitoring in the NICU

- Conventional EEG
  - Pro: Gold standard
  - Con: Limited access to techs, interpretation
- aEEG
  - Pro: Apply and interpret at bedside, track trends
  - Con: Lower sensitivity and specificity for seizures
EEG for Prognosis in HIE

- cEEG
  - Burst suppression or low voltage poor prognosis >48 hrs
- aEEG
  - Normalization of record by 48 hrs good prognosis

Nash et al. 2011, Thoresen et al. 2010

Burst Suppression EEG

Neonatal Seizures

- Neonatal brain predisposed to seizures
  - Excitation predominates in neuronal networks
  - Inhibition relatively underdeveloped
- Incidence seizures 22-64% in mod-severe HIE
  - Decreased by hypothermia?
- Increasing evidence seizures increase neurologic injury

Focal Seizure

Rhythmic sharp waves in left hemisphere associated with clonic jerking right arm and leg

Pinto LC and Gilbert P 2001

Case 2

- EEG: seizures confirmed, burst-suppression background
- Extensive neurometabolic and genetic lab evaluations (blood, urine, CSF)
- Brain MRI normal
- Multiple anticonvulsant medications
  - Phenobarbital, levetiracetam, lorazepam
  - Seizures controlled on therapeutic phenytoin

Neonatal Epileptic Encephalopathies

- Inborn errors of metabolism
  - Nonketotic hyperglycinemia (glycine encephalopathy)
  - Sulfite oxidase/molybdenum cofactor deficiency
  - Phenylalanine or tyrosine deficiency
  - Folic acid responsive syndrome
  - Werner's disease
  - GABA transaminase deficiency
  - GLUT-1 deficiency syndrome
  - Peroxisomal disorders
  - Mitochondrial disorders
  - Organic acidemias
- Structural brain malformation
  - Focal or multifocal cortical dysplasia
  - Hemimegalencephaly
- Infantile epileptic encephalopathies
  - Channelopathies
  - Other gene mutations
Case 2 Follow Up

- Infantile epilepsy gene panel identified a clinically significant gene mutation
- At 18 months, she is seizure free on medication and has mild global developmental delay

Case 3

- Term baby boy, NSVD at home
- Perinatal depression: poor respiratory effort, received bag-mask ventilation, Apgars 4,6,8
- Seizures began at 1½ hrs of life (bicycling, lipsmacking) sodium 119, loaded phenobarbital
- Subsequent seizures within first 12 hrs of life
  - tongue thrusting, lip smacking, rhythmic jerking both arms and legs, clonic left arm only
Case 3

- Exam: decreased movement and low tone of L arm
- EEG: initially discontinuous but normal by 2nd day of life, no epileptic activity
- Next diagnostic study?

Goals of Neonatal Neuroimaging

- Etiology of brain injury
- Evolution of brain injury
- Monitor effect of intervention
- Prognosis for future neurodevelopment

Imaging Modalities: Pros and Cons

- Head Ultrasound
- Head CT
- Brain MRI
Brain MRI in HIE

- Brain MRI
  - Signal abnormalities on T1/T2 sequences appear 3-4 days and best seen >7 days after injury
- Diffusion-weighted imaging
  - Sensitive for acute ischemia
  - Diffusion abnormalities most prominent 24-96 hrs of life
  - Pseudonormalization 6-8 days (>10 days if cooled)
- MR spectroscopy
  - High lactate within few hrs, NAA declines in days-week
  - Severity of changes correlates with severity of brain injury

MRI for Prognosis

- Presence and severity of brainstem injury strongest predictor of neonatal death
- Abnormal signal posterior limb of internal capsule predicts inability to walk independently by 2 years
  - Sensitivity 0.92, specificity 0.77
- MRI after hypothermia remains accurate predictor

Case 3

- MRI: acute stroke in right MCA territory
Perinatal Stroke

- Focal or multifocal disruption in cerebral blood flow
  - Arterial or venous
  - Thrombosis or embolization
- Age between 20 weeks fetal age to 28 days postnatal age
- Confirmed by neuroimaging or neuropathological studies
- Symptoms in neonates
  - Seizures
  - Encephalopathy
  - Abnormal neurologic examination

Perinatal Arterial Stroke

- Incidence:
  - As high as rates of large-vessel arterial strokes in adults
  - >1:2500-4000 live births
  - 90% occur within first week of life
- Risk factors for perinatal stroke
  - Infection, complex congenital heart disease, preeclampsia, maternal drug use, traumatic delivery, inherited or acquired defect in coagulation, placenta pathology
- Recurrence rate <3%


Case 3 Follow Up

- Remaining NICU course
  - Sodium normal by second day of life
  - No seizures after 12 hrs of life
  - Normal exam, weakness resolved by day 3
- At 19 months, mild left arm weakness and seizure-free
Conclusions

- Causes of neonatal encephalopathy are diverse
- History, clinical examination and special diagnostic studies all contribute to determining the underlying diagnosis
- Effective treatments require recognition of the syndrome of neonatal encephalopathy and specific diagnosis of underlying etiology
- Newborn nurses have a critical role in recognizing encephalopathy in their patients

References-1


References-2