Changing Pattern of Brain Injury in the Term Infant

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I have no Financial Disclosures or Conflicts of Interest Relevant to this Presentation
Perinatal brain injury in term infants remains a significant clinical problem and an important cause of perinatal mortality and morbidity.

The most common identified problem has been hypoxic-ischemic encephalopathy

Other causes include symptomatic intracranial hemorrhage and focal cerebral infarction.

Recently we have perceived a change in the pattern of perinatal brain injury.
Is this Perceived Observation Important?

• Prevention
• Treatment
Methods

We undertook a retrospective chart review in order to characterize the incidence, etiology, clinical manifestations and outcome of term infants who are admitted to intensive care with symptomatic perinatal brain injury.
Methods (cont)

• Perinatal characteristics - including FTHR tracings, clinical symptoms, neuroimaging, EEG, and placental pathology.

• **Perinatal depression** was defined as need for face-mask ventilation ± intubation and/or hypotonia.

• **HIE** was defined as low Apgar Score at 10 minutes ± fetal acidemia, need for CPR and subsequent encephalopathy.
Results

• Jan 2004 - Dec 2009 there were 29,597 term deliveries
• 33/29597 (1.1/1000) presented with symptoms potentially attributed underlying brain injury
• Incidence of symptomatic perinatal brain injury
  - HIE                              0.27/1000
  - IVH/IPH                         0.17/1000
  - Subdural Hemorrhage             0.34/1000
  - Focal Cerebral Infarction       0.14/1000
Specific Intracranial Lesions Identified

- Focal Cerebral Infarction
- Intraventricular Hemorrhage
- Intraparenchymal Hemorrhage
- Hypoxic-Ischemic Changes
- Focal Cerebral Infarction
- Subdural Hemorrhage
### Clinical and Pathological Characteristic of the Intracranial Lesions

<table>
<thead>
<tr>
<th></th>
<th>HIE (n=8)</th>
<th>Stroke (n=4)</th>
<th>IPH/IVH (n=5)</th>
<th>SDH (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight [g]</td>
<td>3198 ± 430</td>
<td>3561 ± 248</td>
<td>3257 ± 287</td>
<td>3401 ± 527</td>
</tr>
<tr>
<td>Gestational Age [wks]</td>
<td>38 ± 1.2</td>
<td>40 ± 1.0</td>
<td>39 ± 1.1</td>
<td>40 ± 0.7</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>7/8 (88%)</td>
<td>2/4 (50%)</td>
<td>3/5 (60%)</td>
<td>6/10 (60%)</td>
</tr>
<tr>
<td>In vitro fertilization</td>
<td>3/8 (38%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>3/8 (38%)</td>
<td>2/4 (50%)</td>
<td>2/5 (40%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>Maternal Fever</td>
<td>4/8 (50%)</td>
<td>2/4 (40%)</td>
<td>3/5 (60%)</td>
<td>6/10 (60%)</td>
</tr>
<tr>
<td>Meconium-stained AF</td>
<td>6/8 (75%)</td>
<td>1/4 (25%)</td>
<td>1/5 (20%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>FHR abnormality</td>
<td>4/8 (50%)</td>
<td>2/4 (40%)</td>
<td>1/5 (20%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Cesarean section Delivery</td>
<td>4/8 (50%)</td>
<td>3/4 (75%)</td>
<td>2/5 (40%)</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>Vacuum Extraction</td>
<td>2/8 (25%)</td>
<td>0</td>
<td>0</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>Intubation in DR</td>
<td>4/8 (50%)</td>
<td>1/4 (25%)</td>
<td>0</td>
<td>3/10 (30%)</td>
</tr>
<tr>
<td>CPR in DR</td>
<td>3/8 (38%)</td>
<td>1/4 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cord arterial pH</td>
<td>7.06±0.18</td>
<td>7.16±0.09</td>
<td>7.06±0.08</td>
<td>7.20±0.11</td>
</tr>
<tr>
<td>10 Min Apgar Score ≤ 5</td>
<td>2/8 (25%)</td>
<td>1/4 (25%)</td>
<td>0</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Apnea</td>
<td>2/8 (25%)</td>
<td>0</td>
<td>4/5 (80%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Clinical Seizures</td>
<td>6/8 (67%)</td>
<td>3/4 (75%)</td>
<td>1/5 (20%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>EEG Seizures</td>
<td>3/6 (50%)</td>
<td>3/3 (100%)</td>
<td>2/5 (66%)</td>
<td>0/5</td>
</tr>
<tr>
<td>Histologic Chorioamnionitis</td>
<td>2/5 (40%)</td>
<td>0/4</td>
<td>1/3 (33%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>Fetal Vasculopathy</td>
<td>0/5</td>
<td>3/4 (75%)</td>
<td>1/3 (33%)</td>
<td>0/5</td>
</tr>
<tr>
<td>Abnormal Outcome/ Died</td>
<td>6/8 (66%)</td>
<td>1/4 (25%)</td>
<td>0/4</td>
<td>0/5</td>
</tr>
</tbody>
</table>

Bold = Statistically significant  P<0.05
## Neuroimaging and Clinical Findings

(n=33)

<table>
<thead>
<tr>
<th>Initial Admission to WBN (n=13)</th>
<th>Initial Admission to NICU (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Clinical Presentation</strong></td>
<td><strong>Initial Clinical Presentation</strong></td>
</tr>
<tr>
<td>Apnea n = 5</td>
<td>Respiratory Depression In DR n=20</td>
</tr>
<tr>
<td>Desaturations n = 3</td>
<td>Seizures n=11</td>
</tr>
<tr>
<td>Seizures n = 4</td>
<td>Apnea n= 2</td>
</tr>
</tbody>
</table>

### Neuro-Imaging Diagnosis

<table>
<thead>
<tr>
<th>IVH/IPH (n=5)</th>
<th>Hypoxic-Ischemic Changes (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus thrombosis (n=1)</td>
<td>Subdural Hemorrhage (n=7)</td>
</tr>
<tr>
<td>Subdural Hemorrhage (n=2)</td>
<td>Focal cerebral infarction (n=2)</td>
</tr>
<tr>
<td>Watershed infarction (n=1)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical seizures were both subtle and overt and were not consistently accompanied by an EEG correlate.

EEG seizures were evident in 50% of patients subjected to continuous EEG monitoring.

Not observed in infants with SDH.

The initial presentation in some infants included apnea, and in one patient, apnea was associated with EEG seizures.

Because of the subtle nature of presentation, including desaturation episodes, it becomes important to consider continuous video EEG monitoring to aid in management.
Placental Pathology

- Histologic abnormalities noted in 16/18 cases included
  - Chorioamnionitis (n=7)
  - Fetal thrombotic vasculopathy (n=5).
- 3/4 infants with focal cerebral infarction had evidence of fetal thrombotic vasculopathy.
Mechanisms of Brain Injury

• Most frequently recognized cause – secondary to interruption of placental blood flow – “asphyxia”.

• Tears in the falx and tentorium or bridging cortical veins, secondary to stretching. This is associated with excessive vertical molding and frontal-occipital elongation of the cranium, resulting in hemorrhage.

• Association with placenta pathology, including infection e.g., chorioamnionitis or thrombosis of the fetal vessels
Brain Injury

Asphyxia
Interruption of Placental Blood Flow

“Trauma”
Tears in the Falx Tentorium Cortical Veins

Placental Pathology
Inflammation Thrombotic Vasculopathy

Clinical Signs
Encephalopathy Hypotonia Seizures Apnea Desaturation
Specific Causes
Hypoxic Ischemic Brain Injury

- Hypoxic-Ischemic brain secondary to interruption of placental blood flow may present in two ways depending on the timing of the insult
- Most data from the developed world indicate that the occurrence of HIE is ~ 1 per 1000 term deliveries
- In our experience ~ 50% present acutely and 50% subacutely.
- **Acute presentation** - history of a sentinel event, low extended Apgar scores, fetal acidemia, need for resuscitation
- **Subacute presentation** - minimal support in the DR, normal cord ABG, often triaged to the well baby nursery
Intrapartum Hypoxic-Ischemic Brain Injury

- **Acute Injury**
  - Sentinel Event
  - Cord pH < 7.00
  - DR resuscitation
  - Low 10 min. Apgar
  - HIE
  - Renal dysfunction
  - Neuro-imaging changes (consistent with HIE)
  - 50%

- **Subacute Injury**
  - Normal Labor
  - Cord pH > 7.00
  - No DR resuscitation
  - Normal Apgar scores
  - HIE
  - Renal dysfunction
  - Neuro-imaging changes (consistent with HIE)
  - 50%
Subacute Brain Injury

• Postulate that the onset is close to the onset of labor
• Auto resuscitation
• Labor then maybe uncomplicated or there maybe FHRT abnormalities (usually not regarded as significant)
Intracerebral/Intraventricular Hemorrhage

- Intracranial Hemorrhage is uncommon.
- Maybe found within the GM, ventricles or parenchyma.
- Thalamus - a common site of bleeding and frequently includes IVH as well.
- Predisposing factors include prior
  - Hypoxia-ischemia
  - Sepsis, and coagulopathy

- Primary IVH is rare in the term infant
- Arises from residual germinal matrix, choroid plexus and thalamus.
- Predisposing factors include
  - Prior hypoxia-ischemia, coagulopathies and AVM.
Clinical Presentation

- Sudden onset of marked neurologic abnormalities - seizures, evidence of ↑ ICP, bulging fontanel or blood in CSF
- Presentation maybe more subtle with apnea, hypotonia and/or subtle seizures
- Neuroimaging i.e. cranial ultrasound, CT or MRI readily establishes the diagnosis.
- The prognosis is often good.
Subdural Hemorrhage

- SDH was the most common lesion identified (0.34/1000)
- Presentation is often a depressed and hypotonic infant
- Clinical seizures are rare
- Outcome is good

Chamnanvanaki et al Pediatric Neurol 2002;301-304
Focal Cerebral Infarction
Acute Neonatal Stroke
Maternal Factors
Pre-eclampsia
Thrombophilia

Intrapartum Factors
Chorioamnionitis

Thrombus
Emboli

Vascular insufficiency

Cerebral Ischemia

Reperfusion

Clinical Signs
Seizures (80%)
Hypotonia
Encephalopathy
Irritability

Apgar score unremarkable
Cord pH unremarkable
Triaged to NBN

Focal Cerebral Infarction in Term Infants (1 in 2300 - 4000)
Infection and/or the fetal inflammatory response as a potential contributing factor to brain injury during hypoxia-ischemia
There is a paucity of data with regard to chorioamnionitis, inflammatory mediator release and neonatal neurologic findings in term infants.
Inflammation and Brain Injury - Clinical Observations

• Chorioamnionitis and/or ↑ cord blood inflammatory cytokines i.e. IL-6, IL-1β and TNF-α concentrations have been associated with white matter injury (WMI) and/or cerebral palsy. Specifically ↑ umbilical cord IL-6 concentration was associated with a six-fold ↑ in WMI.

• The fetal inflammatory response (funisitis) is associated with the highest cytokine levels; this response may be biologically more important than the maternal effects.

Yoon, Am J Obstet & Gynecol 96, 97
Objectives

• Determine which inflammatory cytokines are elevated in symptomatic term newborns exposed to mothers with chorioamnionitis when compared to healthy controls

• Determine the postnatal changes in cytokine concentrations at 3 time intervals from birth to 36 hours

• Determine if any of the cytokines studied are correlated with short term neonatal neurological outcomes
Study Design

Study Period (7/99 to 1/01)
Term Newborns exposed to Clinical Chorioamnionitis
n=1660

95% Asymptomatic
Triaged to NBN
n=1571

5% Symptomatic
Triaged to NICU
n=89

n=18 back to NBN

n=10 No consent

n=61 Enrolled

No consent
Short Term Neurologic Outcomes

**Depression at Birth:**

BMV > 2 min or intubation in delivery room, or Apgar < 6 at 5 min

**Abnormal Neurological Examination:**

Modified Dubowitz Score, normal score: $15 \pm 2$ (mean $\pm$ SD)
- Posture
- Arm traction
- Arm recoil
- Leg recoil
- Popliteal angle
- Head lag
- Abnormal movement

**HIE and/or Seizures:**

HIE defined as Apgar Score < 3 at 5 min + Cord pH < 7.00 + Encephalopathy (Sarnat 2-3) + Non CNS dysfunction following a sentinel event.
### CHARACTERISTICS OF CHORIO INFANTS (n = 61)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>40 ± 0.2</td>
</tr>
<tr>
<td>Birth Weight (grams)</td>
<td>3496 ± 88</td>
</tr>
<tr>
<td>Temperature °C (at 30 min)</td>
<td>37.5 ± 0.1</td>
</tr>
<tr>
<td>Apgar at 5 min Median(25%,75%)</td>
<td>8 ( 6, 9 )</td>
</tr>
<tr>
<td>Cord pH</td>
<td>7.15 ± 0.4</td>
</tr>
<tr>
<td>Abnormal WBC at birth</td>
<td>n=40 (66%)</td>
</tr>
<tr>
<td>Multiple Abnormal WBC</td>
<td>n=28 (47%)</td>
</tr>
<tr>
<td>Positive blood cultures</td>
<td>None</td>
</tr>
<tr>
<td>Days in Hospital</td>
<td>7 ± 1 days</td>
</tr>
</tbody>
</table>
IL-6, IL-8, RANTES IN CORD BLOOD: CONTROL VS CHORIO

**IL-6**

- Control: 0
- Chorio: 1071

**IL-8**

- Control: 0
- Chorio: 2580

**RANTES**

- Control: 95,000
- Chorio: 95,000

* p < 0.05
Changes in IL-6 over the First 36 hrs in Chorioamnionitis Infants

![Bar chart showing changes in IL-6 levels over time.](chart.png)

- **Cord**: 1071 pg/ml
- **6 Hrs**: 1451 pg/ml
- **30 Hrs**: 280 pg/ml

* p < 0.05, 6 hrs vs cord
** p < 0.05, 30hrs vs 6hrs and vs cord
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression at Birth</strong></td>
<td>23</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Abnormal Dubowitz Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Hours</td>
<td>8</td>
<td>13%</td>
</tr>
<tr>
<td>30 Hours</td>
<td>4</td>
<td>6.5%</td>
</tr>
<tr>
<td><strong>HIE and/or Seizures</strong></td>
<td>5</td>
<td>8%</td>
</tr>
</tbody>
</table>
Cytokines and Short Term Neurological Outcome

- **Birth Depression**
  Cytokine concentrations were similar in infants with or without birth depression

- **Abnormal Neurological Exam**
  Only IL-6 was correlated at 6 hours with abnormalities in Modified Dubowitz Score
IL-6 AND MODIFIED DUBOWITZ SCORES AT 6 HOURS OF AGE IN CHORIO INFANTS
IL-6, IL-8, RANTES: No HIE vs HIE
Conclusions

- In infants exposed to chorioamnionitis, there was a spectrum of abnormalities in the neurological exam from normal, to transient hypotonia, to HIE

- IL-6, IL-8 and RANTES were significantly elevated in all infants with Chorio as compared to controls
  - IL6 at 6 hours were correlated with hypotonia by Modified Dubowitz Scores
  - IL6, IL8 and RANTES at 6 hrs were highest in infants that developed HIE and/or seizures
Speculation

Chorioamnionitis → Hypotonia → HIE / Seizures

CYTOKINES
Study Design

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No consent  
\( n=61 \) Enrolled
Summary

• The incidence of clinically symptomatic peripartum brain injury is exceedingly low.
• The occurrence of HIE in this inborn population is much less than reported in the literature and comparable to the other identified lesions.
• Most infants, except for those with HIE, were only identified at potential risk for brain injury within the first day or two of age, as a consequence of clinical signs such as apnea, desaturation episodes, or seizures.
• Placental pathology abnormalities are frequent and maybe linked to perinatal brain injury.
Implications

- These findings limit the potential for prevention or neuroprotection except in infants at high risk for evolving HIE.
- Although MRI constitutes the preferred imaging modality, CT is useful in limited instances, e.g., in infants with early clinical signs of ICP potentially attributable to hemorrhage, where a rapid diagnosis is critical.
- A multidisciplinary approach is important in establishing a prompt diagnosis, thus minimizing the potential for ongoing injury.