Neonatal Encephalopathy and Neurologic Outcomes
The 2014 ACOG/AAP Report

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Disclosure

- I have reviewed medicolegal cases for plaintiff and defense attorneys and have given testimony in deposition and trial.
- I have been and am a consultant and expert witness on behalf of the Department of Health and Human Services in the Vaccine Injury Compensation Program.
The charge was simple and straightforward: “to update the document to the current state of scientific and clinical knowledge relating to neonatal encephalopathy and neurological outcomes”.

The title of this report has been changed…to indicate that an array of developmental outcomes may arise after neonatal encephalopathy in addition to cerebral palsy.”
Neonatal Encephalopathy

Assessment of an Acute Peripartum or Intrapartum Event Sufficient to Cause Neonatal Encephalopathy
Criteria for HIE

- **Difference between 2003 and 2014 criteria**
  - 2003 essential label eliminated
    - Broader perspective may be more fruitful
  - Recognition of reasons for diagnosis
  - No claim that all criteria must be met
  - 2003 “narrow” criteria expanded
    - Blood gas
    - Cerebral palsy
    - Understanding that other factors can contribute
Neonatal Encephalopathy

- A clinically defined syndrome of disturbed neurologic function in the earliest days of life in the infant born at or beyond 35 weeks of gestation manifested by subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes.
Neonatal Encephalopathy

- Incidence
  - 3-8 per thousand live births
- Risk factors – antepartum and intrapartum
  - Studies differ as to relative contribution
  - Not the same as cause
Prevalence, causes, and outcome at 2 years of age of newborn encephalopathy: population based study

V Pierrat, N Haouari, A Liska, D Thomas, D Subtil, P Truffert, on behalf of the Groupe d’Etudes en Epidémiologie Périmatale


Objectives: To ascertain the prevalence of newborn encephalopathy in term live births, and also the underlying diagnoses, timing, and outcome at 2 years of surviving infants.

Design: Population based observational study.

Setting: North Pas-de-Calais area of France, January to December 2000.

Patients: All 90 neonates with moderate or severe newborn encephalopathy.

Results: The prevalence of moderate or severe newborn encephalopathy was 1.64 per 1000 term live births (95% confidence interval (CI) 1.30 to 1.98). The prevalence of birth asphyxia was 0.86 per 1000 term live births (95% CI 0.61 to 1.10). The main cause of newborn encephalopathy was birth asphyxia, diagnosed in 47 (52%) infants. It was associated with another diagnosis in 11/47 cases (23%). The timing was intrapartum in 56% of cases, antepartum in 13%, ante-intrapartum in 10%, and postpartum in 2%. In 19% of cases, no underlying cause was identified during the neonatal course. Twenty four infants died in the neonatal period, giving a fatality rate of 27% (95% CI 17% to 36%). Three infants died after the neonatal period. At 2 years of age, 38 infants had a poor outcome, defined by death or severe disability, a prevalence of 0.69 per 1000 term live births (95% CI 0.47 to 0.91). In infants with isolated birth asphyxia, this prevalence was 0.36 per 1000 term live births (95% CI 0.20 to 0.52).

Conclusions: The causes of newborn encephalopathy were heterogeneous but the main one was birth asphyxia. The prevalence was low, but the outcome was poor, emphasising the need for prevention programmes and new therapeutic approaches.
Neonatal Encephalopathy

- Causes
  - Infection
  - HIE
  - Metabolic disturbance
  - Drug effect
  - Genetic disorder
  - Seizure
Neonatal Encephalopathy

- Periventricular leukomalacia
- Infarction (stroke)
  - Arterial
  - Venous
- Hypoxic-ischemic encephalopathy
  - Near total/profound asphyxia
  - Prolonged partial asphyxia
  - Global/diffuse
Periventricular Leukomalacia

- Present in large minority of VLBW children
- Association with
  - Cerebral palsy (diplegia)
  - Cognitive deficits
  - Attentional problems
  - Social difficulties
Periventricular Leukomalacia

- Initially thought to represent white matter injury
- Now part of “Encephalopathy of Prematurity”
  - White matter
  - Deep gray nuclei
  - Cortex
  - Cerebellum
Encephalopathy of Prematurity

- White matter involvement
  - PVL
    - Deep white matter necrosis
      - Cystic
      - Non-cystic (microscopic → glial scar)
  - Diffuse central white matter
    - Gliosis, ↑ microglia with loss of oligodendrocytes
Types of White Matter Injury
Encephalopathy of Prematurity

- Neuronal involvement
  - Axonal degeneration
  - Loss of subplate neurons
  - Gliosis/neuron loss
    - Thalamus
    - Basal ganglia
    - Cortex
    - Cerebellum
Encephalopathy of Prematurity

- Mechanism of injury
  - Blood supply
    - End artery effect
      - Deep penetrators
      - More superficial short penetrators
      - Anastamoses
    - Immature cerebral blood flow
      - Pressure-passive in sick babies
      - Autoregulation
      - Sensitivity to CO2 changes
Encephalopathy of Prematurity

- Immature oligodendrocytes
  - Impaired antioxidant defenses
    - Free radical attack
  - Excitotoxicity
  - Cytokine injury
- Axons
  - Deficiency due to oligodendrocyte injury
  - Direct necrosis
- Deep gray nuclei
  - Secondary response to white matter injury
Encephalopathy of Prematurity

- Subplate neurons
  - Increased apoptosis
  - Effect
    - Failure of axonal connection

- Cerebellum
  - Poor growth
    - Direct injury
    - Trophic effect?
Encephalopathy of Prematurity

- Motor problems
  - Cerebral palsy
  - Dyspraxia

- Cognitive problems
  - Intellectual disability
  - Learning disability
  - Attention/executive dysfunction
  - ?ASD
Periventricular Leukomalacia
Periventricular Leukomalacia
Periventricular Leukomalacia
PVL – Diffuse Injury
Perinatal Stroke

- Definition
  - “a group of heterogeneous conditions in which there is a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies”
Perinatal Stroke

- Incidence - 1/2300 to 1/5000 births
- Male > Female
- Black infants > white infants
- Left > right hemisphere
  - Usually MCA
- 15% with prematurity
Perinatal Stroke

- Arterial
  - Usually MCA
  - Cortical involvement
  - More commonly on left side
- Presentation
  - >50% within 1-3 days of birth with:
    - Seizures
    - Lethargy
    - Poor feeding
    - Hypotonia
Perinatal Stroke

- Venous
  - Highest incidence in newborn period
    - 1/2500
  - Usually superficial and lateral sinuses
    - Deep venous system less common
    - 30% infarction (often hemorrhagic)
- Presentation
  - 70-80% with seizures
  - Lethargy
  - Increased ICP
  - <10% with focal signs
Figure 1. Perinatal stroke syndromes. (A) Acute symptomatic neonatal arterial ischemic stroke. A term neonate seized at 12 hours of age and magnetic resonance imaging revealed restricted diffusion in the middle cerebral artery (MCA) territory on diffusion-weighted imaging (left) and apparent diffusion coefficient analysis (center). Follow-up imaging demonstrates cystic encephalomalacia (right). (B) Arterial presumed perinatal ischemic stroke. Arterial MCA infarctions that are asymptomatic in neonates present later and can involve the entire MCA territory (left), occlusion of the distal M1 with sparing of basal ganglia (center), or divisions of the MCA (right). (C) Periventricular venous infarction also presents as presumed perinatal ischemic stroke, with focal lesions of the periventricular white matter (left and center) and atrophy of the ipsilateral cerebral peduncle (right).
Neonatal CSVT - MRI
Neonatal CSVT - Vasculature
Perinatal Stroke Outcome

- **Motor function**
  - **Stroke type**
    - Arterial 30-60%
    - CSVT 30-50%
  - **Hemiplegia**
    - Hemisphere, internal capsule and basal ganglia
  - **Motor difficulties**
    - PLIC with either basal ganglia or hemisphere
- **Examination**
  - Strength and tone changes
  - Assessment of general movements
Perinatal Stroke Outcome

- Cognition
  - Usually normal
  - Speech delay, learning and attention problems based on hemispheric involvement
  - Decline in full scale IQ with deficits in:
    - Nonverbal reasoning
    - Working memory
    - Processing speed
    (Westmacott et al 2009)
  - No decline unless history of epilepsy
    (Ballantyne et al 2008)
Perinatal Stroke Outcome

- Epilepsy
  - 30-67%
- Recurrence
  - <5%
- Death
  - <10%
Hypoxic-Ischemic Encephalopathy

- Hypoxemia
  - Decreased O2 in blood
- Ischemia
  - Decreased perfusion with inadequate nutrient delivery (including glucose)
Hypoxic-Ischemic Encephalopathy

- **Mechanism of injury**
  - Failure of protective systems
  - Depletion of energy reserves (ATP)
    - Inadequate oxygen and glucose
  - **Secondary cascade**
    - Excitatory amino acids
    - Apoptosis/mitochondria
    - Reactive oxygen species
    - Inflammation
Hypoxic-Ischemic Encephalopathy

- Mechanism of injury
  - Aggravants
    - Hypotension
    - Hypoglycemia
    - Elevated temperature (before or after birth)
    - Infection/inflammation
    - Research varies with some factors
      - Intrauterine growth retardation?
      - Prior hypoxia?
Mechanism of Hypoxic-Ischemic Injury

- Hypoxia-ischemia
- Anaerobic glycolysis
  - ATP
  - Glutamate
  - Lactate
- Adenosine
- Hypoxanthine
- Xanthine oxidase
- Xanthine
- Oxygen
  - Free radicals
- Intracellular Ca²⁺
- N-methyl-D-aspartate (NMDA) receptor
- Activates lipases
- Activates nitric oxide synthase (NOS)
- Nitric oxide
- Free fatty acids
- Oxygen
  - Free radicals
Hypoxic-Ischemic Encephalopathy

- Cell death
  - Necrosis
    - Cell swelling with inflammatory responses
    - No specific genes/enzymes needed
    - Occurrence over minutes to hours
  - Apoptosis
    - Cell shrinkage without inflammation
    - Death enzymes/genes (p53, caspaces)
    - Occurrence over hours to days
Neonatal Encephalopathy

- Three stages (Sarnat & Sarnat 1976)
  - I – mild
    - hyperalertness, uninhibited Moro and stretch reflexes, sympathetic effects, and normal EEG
  - II – moderate
    - obtundation, hypotonia, strong distal flexion, multifocal seizures, and abnormal EEG
  - III – severe
    - stuporous, flaccid, suppressed brain stem and autonomic functions and abnormal EEG
Neonatal Encephalopathy

- Measures of brain function
  - Physical exam
    - Appearance/head circumference
    - Anomalies
    - Level of consciousness
    - Movement and tone
      - Dependent on brain involvement
    - Evidence of increased intracranial pressure
    - Seizures
HIE – Use of EEG

- **Types**
  - Full channel
  - aEEG

- **Uses**
  - Background
  - Seizures
  - Prognosis
Neonatal Events

- Seizures
- Apnea
- Jitteriness/tremor
- Benign sleep myoclonus
Neonatal Seizures Types

- Focal clonic
- Multifocal clonic
- Myoclonic
- Tonic
- Subtle
Neonatal Seizures
Causes

- Hypoxic-ischemic encephalopathy
  - Still occur during hypothermia
- Brain malformation
- Perinatal stroke
- Meningitis/encephalitis
- Metabolic disorders
  - Inborn errors
  - Acquired/transient
- Genetic/familial seizures
Neonatal Seizures
Apnea

- Definition: Cessation of respiratory function
- Occurs in premature > term newborns
- Rare as sole seizure manifestation
- Apnea and depressed consciousness can also be due to:
  - Increased intracranial pressure
  - Infection
  - Metabolic disturbance
Jitteriness/Tremor

- Rhythmic and usually rapid repetitive extremity > trunk movement
- Can have exaggerated response to stimulation
- Association with:
  - Hypoxic-ischemic encephalopathy
  - Infection
  - Drug withdrawal
  - Metabolic disturbance
  - Idiopathic
Neonatal Tremors
Neonatal Encephalopathy

- Neonatal signs
  - Apgar score < 5 at 5 and 10 minutes
    - Unlikely if ≥ 7
  - Fetal umbilical artery acidemia
    - pH < 7 and/or BD ≥ 12 mmol/L
    - pH > 7.20 unlikely
    - Continuum of increasing risk
Neonatal Encephalopathy

- Apgar score
  - Differentiate between spontaneous and assisted scores
  - Low 5 and 10 minute scores are associated with an increased, but not absolute, CP risk
    - Relative risk 20-120 range
  - 1 minute score is poor predictor of outcome
    - Some babies need time to transition
### Neonatal Encephalopathy

- **Umbilical blood gas (odds ratio)**

<table>
<thead>
<tr>
<th>pH</th>
<th>Mortality</th>
<th>Morbidity</th>
<th>CP</th>
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<tbody>
<tr>
<td>&lt; 7.00</td>
<td>6.1</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>&lt; 7.10</td>
<td>7.1</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>&lt; 7.20</td>
<td>4.3</td>
<td>2.2</td>
<td>2.3</td>
</tr>
</tbody>
</table>

OR = %affected with/%affected without
Neonatal Encephalopathy

- Umbilical blood gas
  - Caveats
    - Arterial versus venous
    - Effects of cord compression
    - Sample processing (air bubble, heparin effect)
    - Time to sampling (BE most affected)
    - Reason for low pH – respiratory vs metabolic
    - Similar to post delivery arterial gas
      - Time period of improvement
# Blood Gases

## Table 1. Neonatal data

<table>
<thead>
<tr>
<th>Case No.</th>
<th>BW/ GA</th>
<th>Brady</th>
<th>Etiology</th>
<th>Gases* (U/mm Hg)</th>
<th>Apgar</th>
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<tbody>
<tr>
<td>1</td>
<td>3.9/40</td>
<td>10-15</td>
<td>Uterine rupture</td>
<td>7.16/32-16 (60 min)</td>
<td>0/4/4</td>
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<tr>
<td>2</td>
<td>2.6/38</td>
<td>Unknown</td>
<td>Uterine rupture</td>
<td>6.60/140-30 (cord)</td>
<td>0/1/2</td>
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<td>3</td>
<td>3.5/40</td>
<td>18</td>
<td>Uterine rupture</td>
<td>6.70/147-28 (cord a)</td>
<td>1/3/4</td>
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<td></td>
<td></td>
<td>6.90/119-23 (cord v)</td>
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<tr>
<td>4</td>
<td>2.7/40</td>
<td>15</td>
<td>Uterine rupture</td>
<td>7.27/24-15 (30 min)</td>
<td>1/5/7</td>
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<tr>
<td>5</td>
<td>3.2/40</td>
<td>19</td>
<td>Unknown</td>
<td>7.22/51-8 (cord a)</td>
<td>1/4/4</td>
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<td>7.07/35-22 (20 min)</td>
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<tr>
<td>6</td>
<td>3.1/40</td>
<td>15-20</td>
<td>Cord thrombus</td>
<td>7.37/34-5 (cord v)</td>
<td>3/4/5</td>
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<td>7.20/25-18 (37 min)</td>
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<tr>
<td>7</td>
<td>1.9/41</td>
<td>&gt;10</td>
<td>Unknown</td>
<td>6.96/62-18 (cord v)</td>
<td>1/4/5</td>
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<td></td>
<td>6.93/75-17 (cord a)</td>
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<tr>
<td>8</td>
<td>3.4/40</td>
<td>22</td>
<td>Unknown</td>
<td>6.90/66-23 (22 min)</td>
<td>1/2/4</td>
</tr>
<tr>
<td>9</td>
<td>2.7/39</td>
<td>31</td>
<td>Cord rupture</td>
<td>7.07/32-12 (60 min)</td>
<td>0/3/5</td>
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<tr>
<td>10</td>
<td>4.0/40</td>
<td>“Few min”</td>
<td>Unknown</td>
<td>6.80/104-24 (cord a)</td>
<td>0/0/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.90/100-20 (cord v)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3.3/41</td>
<td>46</td>
<td>Unknown</td>
<td>6.81/44 (10 min)</td>
<td>0/2/4</td>
</tr>
</tbody>
</table>

*Gases expressed as pH/pCO₂. Base excess in mEq/L.

**Abbreviations:**
- **Apgar** = Apgar scores at 1/5/10 min of age, respectively
- **Brady** = Duration of bradycardia before delivery (min)
- **BW** = Birth weight (kg)
- **Cord a** = Cord arterial
- **Cord v** = Cord venous
- **GA** = Gestation (weeks)
Neonatal Encephalopathy

- Neonatal signs
  - Neuroimaging evidence on MRI or MRS
    - MRI best modality at this time
    - Distinct patterns
  - Timing
    - 24-96 hr: Timing
    - 7-21 days: Injury
- Multi-organ system dysfunction
Neonatal Encephalopathy

- Multiorgan system dysfunction
  - Usually transient
  - Affects cardiac, renal, liver, blood, GI
- Measures
  - Vital signs
  - Urine output
  - Lab tests
  - Imaging
- Limited correlation with brain injury
Hypoxic-ischemic Encephalopathy

- **Types**
  - Prolonged partial
  - Near total
  - Combinations
  - Variation by gestational age

- **Assessment**
  - US – can demonstrate edema
  - CT – early change by 24 hours
  - MRI
    - DWI – early changes
    - Other images – later
Hypoxic Ischemic Encephalopathy

MRI

- Conventional study
  - Time period for identification of lesions
  - Types of lesions
    - Near total asphyxia
      - Deep gray nuclei
      - Peri-Rolandic white matter
      - Cerebellum
      - Brainstem
    - Prolonged partial asphyxia
      - Watershed pattern
    - Diffuse/global
  - Cell death
    - Swelling
    - Apoptosis
Hypoxic Ischemic Encephalopathy MRI

- Typical acquisitions
  - T1
  - T2
  - DWI/ADC

- Timing
  - Initially - T1 hypointense, T2 hyperintense
  - Later – T1 hyperintense, T2 hypointense
  - DWI/ADC abnormal early through 7-10 days
Hypoxic Ischemic Encephalopathy (HIE) MRI

- Diffusion weighted imaging
  - Measure of random motion of water in tissue
  - Quantification by apparent diffusion coefficient (ADC)
- Injury causes restricted diffusion
- Visual ID within 1-4 days
  - Greater accuracy with measurement of ADC values
- Some lesions are reversible
HIE – Prolonged Partial

Fig. 3. Peripheral pattern of DWI injury. Bright DWI signal involves diffuse regions of white matter and cortex (arrowheads). The margins of the DWI bright lesions are often indistinct.
HIE- Prolonged Partial
HIE - Near Total

Fig. 2. Central pattern of DWI injury. Bright DWI signal involves (A) the posterior limb internal capsule (angled arrows), the ventrolateral thalamus (vertical arrows), and (B) the perirolandic cortex (arrows). The margins of the DWI lesions are often indistinct.
Figure 2  T1 weighted magnetic resonance images of (A) focal injury in an infant with Sarnat stage II neonatal encephalopathy (NE) aged 11 days and (B) global injury in an infant with Sarnat stage III NE aged 12 days. (A) Focal high signal intensity lesions are visible in the lentiform nuclei and thalami, and there is loss of the normal high signal intensity from myelin in the posterior limb of the internal capsule. (B) There are extensive high signal intensity lesions in the lentiform nuclei and thalami, loss of the normal high signal intensity from myelin in the posterior limb of the internal capsule, and abnormal low signal intensity in the white matter with loss of the normal grey/white matter differentiation.
HIE – Near Total
Hypoxic Ischemic Encephalopathy

- Chau et al (2009)
  - Comparison of CT scan, MRI and DWI MRI at age 3 days in neonatal encephalopathy
  - DWI most sensitive
  - All demonstrated most serious patterns of brain injury
Is White Matter Injury a Preterm Issue?

White Matter Injury in Term Newborns With Neonatal Encephalopathy

AMANDA M. LI, VANN CHAU, KENNETH J. POKITT, MICHAEL A. BARGEST, BRIAN A. LUPTON, ALAN HILL, ELLE ROLAND, AND STEVEN P. MILLER


ABSTRACT: White matter injury (WMI) is the characteristic pattern of brain injury detected on magnetic resonance imaging in the premature newborn. Postnatal asphyxial WMI is increasingly recognized in populations of term newborns. The aim of this study was to describe the occurrence of focal postnatal WMI in a cohort of 48 term newborns with encephalopathy studied with magnetic resonance imaging at 72 ± 12 h of life, and to identify clinical risk factors for this pattern of injury. Eleven newborns (23%, 95% CI 11–33%) were found to have WMI (four minimal, three moderate, and four severe). In 10 of the 11 newborns, the WMI was associated with restricted diffusion on apparent diffusion coefficient maps. An increasing severity of WMI was associated with lower gestational age at birth (p = 0.05), but not lower birth weight. Newborns with WMI had milder encephalopathy and fewer clinical seizures relative to other newborns in the cohort. Other brain injuries were seen in three of the 11 newborns: basal nuclear predominant patterns of injury in one and cortical strokes in two. These findings suggest that WMI in the term newborn is acquired near birth and that the state of brain maturation is an important determinant of this pattern of brain injury. (Pediatr Res 60: 85–89, 2006)

However, WMI does not occur exclusively in premature newborns, and is increasingly recognized in some populations of term newborns. Term newborns with congenital heart disease (CHD) seem to be at particularly high risk of WMI, perhaps due to impairments in utero brain development (12–15). Recent in vivo data suggest that newborns with CHD have delayed brain development before cardiac surgery, possibly as a result of impaired cerebral oxygen delivery in utero (15). WMI is also recognized in the setting of term neonatal encephalopathy (NE). In a series of postmortem examinations of term newborns with NE, three of 21 newborns (14%) had small foci of ischemic lesions in the periventricular white matter, in addition to evidence of acute hypoxic-ischemic lesions (16). In newborns with basal ganglia injury in the context of NE, white matter damage is seen on MRI in nearly one half of the cases (17,18). However, the timing of injury and risk factors for WMI in term newborns with NE remain largely unknown.

The aim of this study was to describe the occurrence and radiologic appearance of WMI in the term newborn with NE.

Figure 1. Severity of acute white matter injury. White matter injury (WMI) has a wide range of severity in the term newborn. A–C: Mild WMI: Patient 2 shows mild bilateral WMI with hypointense lesions (arrowheads) on T1-weighted sequence (A) and focal restricted diffusion (arrow) on ADC map (C) in the white matter near the trigone of the left and right lateral ventricles. No abnormalities are detected on T2-weighted sequence (B). D–F: Severe WMI: Patient 8 shows severe WMI with widespread, bilateral signal abnormalities on both T1-weighted sequence (D) and ADC map (F). These lesions are seen on T2-weighted imaging as abnormal signal hypointensities (E). Each mark on the scale bar represents 1 cm.
Hypoxic Ischemic Encephalopathy

MRI

- Concerns
  - Pre-existing lesions
    - Cowan et al describe majority as acute
  - Transport to scanner
  - Acquisition
    - First days for timing
    - Later for extent of abnormality (DWI may track Wallerian degeneration)
  - Effects of hypothermia
Neonatal Encephalopathy

- Consistent contributing factors
  - Sentinel event
    - Ruptured uterus
    - Placental abruption
    - Cord prolapse
    - Maternal cardiovascular collapse
    - Blood loss
Neonatal Encephalopathy

- Consistent contributing factors
  - FHR patterns
    - Category I and II tracing with Apgar ≥ 7 at 5 minutes and/or normal cord ABG not consistent
    - Minimal/absent variability and no accelerations at presentation and > 60 minutes suggests prior problem
  - Suggestive - change from Category I to:
    - Category III
    - Persistent decelerations with ↑HR or ↓variability
Neonatal Encephalopathy

- Electronic fetal monitoring
  - Not consistent with intrapartum HIE
    - Category I or II with normal cord arterial gas and Apgar≥7 at 5 minutes
    - Minimal or absent variability and no accelerations from presentation
  - Consistent with intrapartum HIE
    - Category I at presentation changing to Category III
    - Category I at presentation changing to minimal variability or tachycardia with recurrent decelerations
Cerebral Palsy Litigation: Change Course or Abandon Ship

Thomas P. Sartwelle, BBA, LLB1 and James C. Johnston, MD, JD2

Dereliction of Duty

There is simply no answer to that question. Nor is there an answer to the question of why birth-related professional organizations allowed trial lawyers and their courtroom experts to transform electronic fetal monitoring from a glorified electronic heartbeat counter into a miracle courtroom machine, the magnum opus of obstetrics. Electronic fetal monitoring became the backbone of increasingly large and frequent cerebral palsy verdicts that culminated in today’s international medical liability obstetrical crisis. For 40 years, birth-related professional organizations have had the ability to stop this cerebral palsy—electronic fetal monitoring charade but refused to intervene.

And it is unlikely to occur in the next half-century. Unfortunately, organized medicine has not overcome the well-worn birth-related myths permeating society’s, politicians’, and physicians’ collective unconscious, and medicine is unlikely to overcome trial lawyers’ iron-fisted hold on the birth injury fault-finding tort system.

These expansive evidence codes—along with expanding liability concepts like product liability, mass tort actions, class actions, vicarious liability, and the like—ushered in an era of unprecedented jury verdicts. Trial lawyers put expert witnesses on the world’s witness stands to testify about alleged scientific opinions based on little more than personal beliefs and unpublicized personal data untested by peer review or the scientific method. The era of junk science—‘trust me, I’m a doctor’—resulted in mass tort cases where billions were paid to alleged victims—and primarily their lawyers—based on nothing more than experts’ causation opinions that, when finally tested, were found to be not only erroneous but unscientific. Among dozens of examples are breast implants; Bendectin; pertussis; thimerosal; and measles, mumps, and rubella (MMR) vaccine allegedly causing autism.26 This hit-or-miss justice based on novel scientific theories espoused by “experts” prompted one contemporary observer to write: “Junk science verdicts, once rare, are now common. Never before have so many lawyers grown so wealthy peddling such ambitious reports and the science of the things that aren’t so.”27
Neonatal Encephalopathy

- Consistent contributing factors
  - Consistent type and timing of brain injury patterns
    - MR most sensitive
    - US changes 48 hours or longer
    - CT may not in 24-48 hours
    - Accurate interpretation important
    - Neuroimaging cannot determine etiology
  - No evidence of other contributing factors
Neonatal Encephalopathy

- Causes
  - Infection
  - HIE
  - Metabolic disturbance
  - Drug effect
  - Genetic disorder
Neonatal Encephalopathy

- Infection (sepsis and/or CNS)
  - Bacterial
    - Group B strep
    - E. coli
    - Klebsiella
    - Listeria
  - Viral
    - Herpes simplex
    - Enterovirus
    - Parechovirus
    - Rotavirus
  - Congenital infection
What Can Mimic HIE?

Rotavirus infection

Yeom et al 2015
What Can Mimic HIE?

- Parechovirus infection
- Sulfite oxidase deficiency
Neonatal Encephalopathy

- Placental pathology
  - “Reliable correlations between various placental abnormalities and adverse neonatal outcomes are limited and often conflicting.”
  - “Until controlled studies are available, it is difficult to reach an evidence-based determination whether or to what degree a given placental finding has contributed to adverse outcomes.”
  - Association between clinical chorioamnionitis and cerebral palsy
Neonatal Encephalopathy

- Consistent contributing factors
  - Developmental outcome is spastic quadriplegia or dyskinetic cerebral palsy
    - Other CP subtypes less likely to be associated
    - Other developmental abnormalities may occur
ing at a median age of 10.5 days. We previously showed late changes in WM diffusion parameters 2 to 3 weeks after an acute insult to the BGT, where the WM initially appeared normal. The WM changes seen in the infants with pattern II may well be secondary to the central gray matter injury. Mercuri et al. showed that secondary microcephaly is often associated with WM atrophy and may occur even if overt injury to WM is not seen on very early scans. Only 5 infants with BGT injury on initial scans had optimal head growth in follow-up assessments; these infants had mild or moderate BGT damage only and either developed athetoid CP, had fine motor difficulties, or were considered normal.
motor outcomes at 30 months of age, with the watershed predominant pattern having an intermediate outcome (Table III; Figure). None of the newborns with normal MRI results had an MDI score <70 (2 SD below the mean) or functional motor deficits (neuromotor score ≥3). Eight newborns with the basal ganglia/thalamus pattern (50% of survivors) had an MDI score <70, and 9 newborns with the basal ganglia/thalamus (56% of survivors) had functional motor deficits (spastic quadraparesis in 3, spastic hemiparesis in 1, and spastic triaparesis in 1). Three of the 5 newborns with a watershed pattern and functional motor deficits had isolated watershed injury without deep gray nuclei abnormalities. Of the 32 newborns lost to follow-up at 30 months of age, 20 were examined at 12 months (5 with normal MRI results [16%], 10 with the watershed predominant pattern [16%], and 5 with the basal ganglia/thalamus predominant pattern [19%]); the outcomes at 12 months of this group were similar to that of the cohort observed to 30 months. In the infants evaluated at both times, the MDI of infants with the watershed pattern was significantly lower at 30 months than at 12 months ($P = .0007$), but did not differ with time in the infants with normal MRI results ($P = .5$) or basal ganglia/thalamus
A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy

Ernest M. Graham, MD; Kristy A. Ruis, MD; Adam L. Hartman, MD; Frances J. Northington, MD; Harold E. Fox, MD, MSc

remaining 41%. A review of all consecutive patients diagnosed with cerebral palsy in a single pediatric neurology practice over a 10-year period attempted to use a precise stringent definition for intrapartum hypoxia-ischemia. The diagnosis of intrapartum hypoxia-ischemia required the documentation of moderate-severe neonatal encephalopathy, as defined by Sarnat, with at least 3 of 7 criteria (fourth study in Table 3). They found that perinatal hypoxia-ischemia accounted for 71% of the term infants with dyskinetic cerebral palsy but that intrapartum hypoxia-ischemia as a causal etiology was not restricted just to the spastic quadriplegic and dyskinetic subtypes, which they believe suggests that the criteria proposed by the American College of Obstetricians and Gynecologists and American Academy of Pediatrics, limiting causal attribution of asphyxia to these 2 subtypes, may be too restrictive.

All cases of cerebral palsy have been followed in western Sweden since 1956, and the 3 most recent reports included a definition of intrapartum hypoxia-ischemia. They found that the origin of cerebral palsy in term infants was peri/neonatal in 35%. The overall trend over the 12-year period 1987-1998 was a significant decline in total cerebral palsy prevalence, which decreased to 1.92 of 1000 live births. These studies do not include data on umbilical arterial gases. They thought that the requirement that only dyskinetic and quadriplegic types of cerebral palsy should be considered to have been caused by intrapartum hypoxic events is too conservative. Dyskinetic cerebral palsy and spastic tetraplegic/severe diplegic subtypes occurred in 59% of the children, but mild diplegic and hemiplegic subtypes comprised the remaining 41%. A review of all consecutive...
Does perinatal asphyxia impair cognitive function without cerebral palsy?

F F Gonzalez, S P Miller

Some studies on neurodevelopmental outcomes after neonatal encephalopathy have suggested that cognitive deficits do not occur in the absence of cerebral palsy. It is increasingly apparent that childhood survivors of overt neonatal encephalopathy may have cognitive impairments, even in the absence of functional motor deficits. The risk of cognitive deficits is related to the severity of neonatal encephalopathy and the pattern of brain injury on neuroimaging, particularly the watershed pattern of injury. A better understanding of the risk factors for cognitive abnormalities after neonatal encephalopathy will ultimately lead to interventions to prevent these deficits. Identifying the full spectrum of neurodevelopmental outcomes after neonatal encephalopathy will also allow care givers to identify children requiring early intervention to maximise their potential for independent function throughout development.
### Table 2 - Physiological variables

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<tr>
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<th>Limited PSI</th>
<th>Extensive PSI</th>
<th>Normal MRI</th>
<th>p</th>
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<tbody>
<tr>
<td>Blood glucose (mg/dL)&lt;sup&gt;a&lt;/sup&gt;</td>
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| < 30                     | 4 (36%)     | 1 (14%)       | 0          | 0.046
| 30 to ≤ 40              | 3 (27%)     | 2 (29%)       | 0          | < 0.05 L vs. N (Tukey test) |
| > 40                    | 4 (36%)     | 4 (57%)       | 9 (100%)   |      |
| Hepatic dysfunction<sup>b</sup> | 6<sup>d</sup> (55%) | 0            | 0<sup>c</sup> | 0.0037 |
| Renal dysfunction<sup>b</sup> | 5<sup>c</sup> (45%) | 1 (14%)      | 0<sup>c</sup> | 0.044 |
| Mechanical ventilation<sup>b</sup> | 4 (36%)     | 5 (71%)       | 6 (57%)    | NS   |
| Neonatal seizure<sup>b</sup> | 11<sup>d</sup> (100%) | 7<sup>c</sup> (100%) | 0<sup>d</sup> | < 0.001 |
| Onset of neonatal seizure<sup>a</sup> |             |               |            |      |
| < 24 h                   | 6 (55%)     | 4 (57%)       |            | NS   |
| 24 h to < 48 h           | 3 (27%)     | 2 (29%)       |            |      |
| 48 h to < 72 h           | 0           | 0             |            |      |
| > 72 h<sup>e</sup>      | 2 (18%)     | 1 (14%)       |            |      |
| Acute stage EEG abnormalities<sup>a</sup> |             |               |            |      |
| None                     | 0           | 0             | 3 (33%)    | 0.030
| Minimal                  | 1 (9%)      | 0             | 1 (11%)    | < 0.05 L vs. N (Tukey test) |
| Mild                     | 1 (9%)      | 1 (17%)       | 2 (22%)    |      |
| Moderate                 | 5 (45%)     | 1 (17%)       | 2 (22%)    |      |
| Marked/maximal           | 4 (36%)     | 4 (57%)       | 1 (11%)    |      |
| Deterioration of ASA<sup>b</sup> | 3 (33%)     | 3 (60%)       | 0          | NS   |
| Mental retardation<sup>b</sup> | 5 (45%)     | 7<sup>d</sup> (100%) | 1<sup>d</sup> (11%) | 0.0619 |
| Cerebral palsy<sup>b</sup> | 2 (18%)     | 7<sup>d</sup> (100%) | 1<sup>d</sup> (11%) | < 0.001 |

NS: not significant. ASA: acute stage EEG abnormalities; L: Limited PSI; E: Extensive PSI; N: Normal MRI; KW: Kruskal-Wallis.
Neonatal Watershed Brain Injury on Magnetic Resonance Imaging Correlates With Verbal IQ at 4 Years
Kyle J. Steinman, Maria Luisa Gorno-Tempini, David V. Glidden, Joel H. Kramer, Steven P. Miller, A. James Barkovich and Donna M. Ferriero
Pediatrics 2009;123;1025-1030

provide inaccurate results. To address the question of association between specific brain regions injured and domain-specific cognitive outcomes, we therefore limited our study to subjects with no functional motor impairment (NMS < 3). Given this, our findings must be interpreted with caution in children with functional motor deficits.

<table>
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<tr>
<th>TABLE 4</th>
<th>Subject Characteristics by 4-Year VIQ Groups and Total</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td>VIQ &lt; 70 (n = 6)</td>
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<tr>
<td>Male gender</td>
<td>4 (67)</td>
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<tr>
<td>Gestational age, wk</td>
<td>40 (35–42)</td>
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<tr>
<td>Cesarean section</td>
<td>4 (67)</td>
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<tr>
<td>Birth weight, g</td>
<td>3605 (2350–5120)</td>
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<tr>
<td>Birth head circumference, cm</td>
<td>35.5 (31–36)</td>
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<tr>
<td>5-min Apgar</td>
<td>4.5 (4–6)</td>
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<tr>
<td>Encephalopathy score (0–6)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 (2–6)</td>
</tr>
<tr>
<td>Resuscitation score (1–6)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 (4–6)</td>
</tr>
<tr>
<td>Neonatal seizures</td>
<td>1 (17)</td>
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<tr>
<td>PIQ</td>
<td>87 (71–102)</td>
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and motor outcomes at 30 months. In contrast, in the whole cohort, those with mostly WS pattern of injury had cognitive impairments less severe than those with the BG pattern and did not have motor impairments.
Neonatal Encephalopathy

- Limitations
  - Competence of clinicians
  - Medical literature
  - Limited discussion of interaction of contributing factors
  - Report internal consistency
  - Are correct questions being asked?
    - EFM – screen or diagnosis, pattern types