Perinatal Causes of Cerebral Palsy

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Objectives

• Discuss the historical perspectives regarding the etiology of cerebral palsy.
• Discuss the epidemiology and clinical presentation of cerebral palsy.
• Describe the potential role of birth weight and premature birth on the development of cerebral palsy.
• Identify the risk multiple gestation pregnancies on the incidence of cerebral palsy.
• Discuss the role of placental pathology and cerebral palsy.
• Identify the mechanism of brain damage caused by hyperbilirubinemia and kernicterus.

CP: Definitions

• Cerebral Palsy
  – Refers to a group of non-progressive disorders of movement and posture which cause activity limitations
  – Motor disturbances often accompanied by
    • Sensorineural deficits and functional disability
      – Disturbances of sensation
      – Cognition, communication, perception limitations
      – Behavioral issues
      – Seizure disorder

• International Classification of Functioning
  – Describes child’s health/well-being in terms of
    • Body structures – organs & limbs
    • Body functions – physiologic functioning
    • Activities – learning, communicating, walking
    • Participation – involvement in family, community life
    • Environmental facilitators – day care, education
    • Environmental barriers – negative attitudes, discrimination, lack of comprehensive insurance

• Cerebral Palsy has classically been separated by findings of spasticity
  – Spastic diplegia
    • Primarily affecting the lower limbs
  – Spastic hemiplegia
    • Affecting one side of the body
  – Spastic quadriplegia
    • Affecting all limbs
  – Choreaathetoid
    • Affecting extrapyramidal pathways of basal ganglia

• Cerebral Palsy
  – Prevalence
    • ~ 2.5 per 1,000 live births
    • Affects 1 in 5 school-aged children
    • Stable over past 40 years
    • Remarkably similar in developed countries
    • Modest increase in noted in VLBW infants
    • Approximately half of all cases develop after full-term births (36 wks) following an apparent normal gestation

• Term and Preterm Presentation
  – Term Presentation
    • ~ 50% of CP cases occur in infants born after 37 weeks of gestation; the other 50% occur in the approximately 10% of babies born preterm
  – Preterm Presentation
    • The relative risk of CP increases steadily with decreasing gestational age at birth
    • At the lowest gestational ages at which survival now occurs, the risk of CP is 5% to 15% or at least 50 times the risk of infants born at term

Paneth, N, et al. NeoReviews, 2005;vol.6, no.3, e133


• Neuro-Imaging of Children with CP
  – Nearly universal finding white matter loss in the periventricular regions of the brain
  – 10% and 15% of children who have CP have a recognizable malformation of the brain, such as schizencephaly, that must have evolved prior to the third trimester
  – Basal ganglia and thalamic damage is not rare
  – 10% to 20% of children have no recognizable abnormality on MRI or CT

Paneth, N, et al. NeoReviews, 2005;vol.6, no.3, e133


• William John Little (1810-1894)
  – Developed term “apoplexy” or “congenital paralysis”
  – Suggested association between birth injury, perinatal asphyxia and CP
  – Described congenital hemiplegia as a consequence of preterm birth
  – Hypothesized inadequate supply of “oxygen and materials for nutrition” and “insufficient removal of carbon and other residues”

• William Osler (1849-1919)
  – Agreed with Little that injury “usually dates from birth”
  – Introduced the phrase “cerebral palsy” to describe the “non-progressive neuromuscular disease in children”
  – Favored hypothesis of trauma, but stressed “it was nearly impossible to be sure about the causes of CP”

• Sigmund Freud (1856-1939)
  – Agreed with Little on role of asphyxia and birth trauma
  – Provided a comprehensive classification system for CP
  – Looked for causes of CP beyond the immediate intrapartum period
  – Also suggested it may be “congenital” from “deeper effects influencing the development of the fetus”
Timing and Possible Etiologies of Insult
- Antepartum period 70-80% of cases
  - Chromosomal abnormalities, placental pathology, multiple gestation, prematurity, LBW, perinatal infection
- Intrapartum period 20% of cases
  - Perinatal trauma, multiple gestation, intrapartum asphyxia, prematurity, LBW, perinatal infection
- Postnatal 10% or less of cases
  - Intrapartum asphyxia, hyperbilirubinemia, neurometabolic diseases, prematurity, LBW, perinatal infection

Chromosomal Anomalies
- ~10% of CP from chromosomal anomalies
- > 30,000 genes are expressed in the brain
- Major duplications or deficiencies are lethal
  - Trisomy 16 – most common trisomy, but lethal
  - Trisomy 13 – only 2.8% are live born infants
  - Trisomy 18 – only 5.4% are live born infants
  - Trisomy 21 – only 23.8% are live born infants
- Familial clustering is rare in CP
  - Suggesting that genes by themselves do not play a large role in CP

Placental Function
- "Sole Supply Line" and "Main Barrier"
  - Adaptive responses identified in the placenta
    - Attempts to ameliorate adverse environment
      - Increased NRBC's, chorioangiosis
        - Hyperinsulinemia → placental overgrowth
    - Lesions affecting the placenta/fetus
      - Uteroplacental vascularature
      - Fetoplacental vascularature
      - Inflammation

Placental Lesions

<table>
<thead>
<tr>
<th>Sentinel Lesions</th>
<th>Decreased Placental Reserve</th>
<th>Thrombo-inflammatory Processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uteroplacental separation</td>
<td>Chronic patterns of limiting compensation</td>
<td>Fetal thrombotic vasculopathy</td>
</tr>
<tr>
<td>Fetal hemorrhage</td>
<td>Chronic maternal under-perfusion</td>
<td>Chronic villitis</td>
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<tr>
<td>Umbilical cord occlusion</td>
<td>Chronic abortion</td>
<td>Meconium-associated vascular necrosis</td>
</tr>
<tr>
<td>Amniotic fluid embolism</td>
<td></td>
<td>Choriamnionitis with vasculitis</td>
</tr>
</tbody>
</table>

Multiple Gestation
- Recognized by Freud as a risk factor
- Greater proportion multiples - preterm or LBW
- Infants of BW < 1500 grams comprise
  - 0.9% of singletons
  - 9.4% of twins
  - 32.2% of triplets
  - 73.3% of quadruplets
- Shift to left in BW → ↑ prevalence of CP
  - < 2500 gm no significant increase in risk
  - ≥ 2500 gm significant 3-4 fold increase risk

Multiple Gestation
- Factors peculiar to process of multiple gestation pregnancies
  - Surviving twin phenomena
    - Associated with severe morbidity in survivor
    - Risk of injury 1:10 in multiples vs. 1:400 of all births
    - Risk of CP even greater when both twins are live births and one dies in infancy
  - Injuries include
    - Multicystic encephalopathy or porencephaly
    - Ventriculomegaly, cerebral infarction
    - Monochorionicity is key risk feature
• Monochorionicity
  – Common component when fetal demise in one twin and CP in surviving twin

• Theories
  – Embolic
    • Thromboplastin-like substances
  – Ischemic
    • Shunting into low-resistance fetus
  – Hemodynamic instability
    • Bidirectional shunting → ischemic damage → affects either/both fetuses

Pharoah, POD Clinics in Perinatology 2006; vol 33; no 2; 301-313.

• Intrapartum Asphyxia
  – Occurs during first & second stages of labor
  – 2º to interruption of placental blood flow
    • Impaired gas exchange → hypoxemia → hypercapnia
    • Often identified by fetal acidosis (? pH < 7.0)
    • Redistribution of fetal cardiac output
    • Loss of cerebral vascular autoregulation
    • Progressive ↓ in CO with ↓ CBF

Pharoah, POD Clinics in Perinatology 2006; vol 33; no 2; 301-313.

• "Sentinel Event" Inclusion Criteria (AAP/ACOG)
  – Intrapartum Asphyxia (requires a minimum of the following)
    • Evidence of antepartum or intrapartum insult
      – Fetal HR abnormalities, thick meconium, ↓ BPP
      – Depression at birth → need for resuscitation
      – Prolonged assisted ventilation (> 10 minutes)
      – Low APGAR score (< 5) at 10 minutes
      – Cord pH ≤ 7.00; Base deficit ≥ 16
    • Evidence of neonatal encephalopathy
      – Alterations in tone, consciousness, reflexes
      – Usually with multisystem involvement
      – May or may not result in permanent neurologic impairment

Perlman, JM Clinics in Perinatology 2006; vol 33; no 2; 335-353.

• Intrapartum Asphyxia
  – Clinical Measures of Asphyxia
    • FHR Monitoring
      – 3 decade experience has demonstrated minimal impact on subsequent neurologic outcome
      – Incidence of seizures may be reduced
      – Long term neurologic & cognitive outcome is unaffected
    • MSAF
      – Affects 10-20% of infants
      – ? Of relationship to fetal stress
      – No association with regard to asphyxial process, duration of event or outcome

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• Intrapartum Asphyxia
  – Clinical Measures of Asphyxia
    • CPR
      – Need for CPR significantly ↑’s risk for abnormal outcome
      – Implies failure of fetal adaptive mechanisms
    • Apgar Score
      – Inappropriate to use to define birth asphyxia in isolation
      – Persistent low Apgar score at 5, 10, 20 minutes despite resuscitation is associated with ↑’ing mortality & morbidity
      – Low 5 minute Apgar score (< 5) + fetal acidemia (pH < 7.0) + need for intubation or CPR indicative of significant intrapartum insult
      – Such infants are 340-fold more likely to progress to moderate to severe encephalopathy

Perlman, JM Clinics in Perinatology 2006; vol 33; no 2; 335-353.

• Perinatal Trauma
  – Injuries sustained by infant during labor & delivery primarily as a result of mechanical forces
  – Actual incidence difficult to ascertain
  – Incidence sharply ↑’s with instrumented delivery
  – Role of ↑ C/S delivery rate (31.2%)”
  – Significant reduction in traumatic CNS injuries over past 20 years

Perlman, JM Clinics in Perinatology 2006; vol 33; no 2; 335-353.
• Perinatal Intracranial Injuries
  – Subdural hemorrhage
    • SVD 1.0-2.9 per 10,000 births
    • Vacuum or forceps 7 to 9.8 per 10,000
    • † Incidence in instrumented deliveries, older mothers, dysfunctional labor
  – Epidural hemorrhage
    • Rare in newborn; "trauma-related" phenomena
  – Intraparenchymal hemorrhage
    • Rarely an isolated phenomenon
    • Associated with depressed skull fractures, subarachnoid hemorrhages, epidural hematomas

• Perinatal Extracranial Injuries
  – Subarachnoid hemorrhage
    • Associated with instrumented deliveries, skull fractures
  – Skull fractures
    • Linear or depressed; usually on parietal bone
    • Most commonly an isolated phenomena
  – Subgaleal hemorrhage
    • Hemorrhage of aponeurotic layer
    • Incidence 4-60 per 10,000
    • Association with vacuum extraction, dragging shear

• Hyperbilirubinemia and Kernicterus
  – Excellent correlation between etiology, pathogenesis, and clinical symptoms
  – Basal ganglia involvement
  – Central auditory pathology

• Bilirubin
  – Result of normal physiologic processes
  – Clearance is a placental function in utero
  – Immaturity of liver & intestinal processes for metabolism, conjugation, excretion
  • ? Role as an anti-oxidant
  • ? Role in oxygen-rich transitional physiology
  – Neurotoxic at a cellular level

• The Pilot Kernicterus Registry
  • 80 US babies enrolled from 1984-1998
  – Factors
    • All discharged < 72 hrs after birth
    • 60% were term gestation
    • 65% breastfeeding
    • 67% were males
    • TB levels at ranged 26-50 mg/dl
  – Sentinel alerts issued
  – Policy statements
  – Practice guidelines

• Prediction & Prevention of “Dangerous” Hyperbilirubinemia
  – Predictors for TSB >25 mg/dl (73/51,387; 0.14%)
    • Early jaundice …………………Odds Ratio = 7.3
    • Family history: …………………Odds Ratio = 6.0
    • Exclusive breast feeding ………Odds Ratio = 5.7
    • Bruising …………………Odds Ratio = 4.0
    • Asian race ……………………Odds Ratio = 3.8
    • Cephalhematoma …………Odds Ratio = 3.3
    • Maternal age …………………Odds Ratio = 3.1
    • Lower gestation …………Odds Ratio = 0.6/wk
  – Conclusions: Prevention may require a closer follow-up than presently recommended by AAP


Kernicterus as “Never Event”
**Acute Bilirubin Encephalopathy**

- Phase 1
- Lethargy
- Poor feeding
- Hyperactive movements
- High-pitched cry
- Possible seizures

**Chronic Bilirubin Encephalopathy**

- Phase 2
- Seizures
- Respiratory failure

**Kernicterus**

- Lethargy
- Irritability
- Inconsolability
- Occurs after 1st year
- Poor feeding
- Apnea, fever
- No feeding
- High frequency hearing loss

**Phase 3**

- Hypotonia
- Hypertonia
- Bicycling movements
- Persistent upward or horizontal gaze
- High-pitched cry
- Oculogyric crisis

**Possible sequelae**

- Hypotonia
- Hypertonia
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**Retrocolis, opisthotonus**

**Coma**

**Dental dysplasia**

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We need a bigger boat!

Roy Schieder, JAWS

**Acute Bilirubin Encephalopathy**

- Functional immaturity of the late preterm infant may obscure the clinical symptoms of acute bilirubin encephalopathy
- These infants are at greater risk for Kernicterus and BIND (Bilirubin Induced Neuronal Dysfunction)

**Prematurity + LBW**

- Inflammation
- Cell/Tissue Injury
- Intraventricular Hemorrhage
- Periventricular Leukomalacia
- Chronic Lung Disease/BPD
- Retinopathy of Prematurity
- Necrotizing Enterocolitis

- Prematurity and LBW
  - Schmidt, et al
  - Examined 3 neonatal complications (BPD, parenchymal brain injury, severe ROP) n 910 infants with BW < 1,000g
    - In survivors at 18 months 13% had CP; 26% had developmental disability
    - CP rates ↑ to 36% for those with IVH grade 3 or 4, ventriculomegaly, or cystic PVL
    - 24% of those with severe ROP (Stage 4 or 5) had CP
    - 17% with BPD (supplemental O2 at 36 wks) had CP
    - If free of these morbidities rate of death or developmental impairment at 18 months was 18%
    - If all three impairments present the rate of death or neurodevelopmental disability was 86%

- Prematurity and LBW
  - Stoll, et al
  - Role of postnatal infection on ND impairments
  - 6,093 survivors with BW between 401 – 1,000g
  - Born in US between 1993 -2001
    - Infants who did not have infection (n=2161)
    - Infants who had clinical infection + IV antibiotics (n=1538)
    - Infants who had sepsis (n=1922)
    - Infants who had NEC (n=279)
    - Infants who had meningitis (n=193)
    - 2/3rds of survivors had post natal infections
    - 1 in 5 of survivors who had sepsis, NEC, or meningitis had CP and high rate of cognitive disability

- Prematurity and LBW
  - Hintz, et al
  - Impact of NEC on ELBW survivors compared to survivors who did not have NEC
    - 1 in 4 who had surgically managed NEC had CP
    - > than 2 in 5 had developmental disability
    - Rates of CP were 12% in children without NEC
    - Impact of NEC is more than gastroenterological and has sustained contributions to neuromotor and cognitive disability
• **Intrauterine Growth**
  - Defined as increase over time in fetal growth
  - Growth velocity (mm/wk) vs. relative size (wt/GA)
    - “Optimum BW” ~ 1 SD heavier than average
    - At all gestations infants either smaller or heavier than this have progressively ↓ risk of CP
    - Rate for males is statistically greater than for females
    - ? Risk factor → abnormal growth → CP
    - ? Abnormal growth → risk factor → CP
  - Is CP a consequence or a cause of growth deviation or an associated phenomena?

• **Prematurity + LBW + Infection/Inflammation**
  - Maternal Infection and Risk of Preterm Birth
    - ~25% of all preterm births associated with maternal infections
    - Risk of infection increases as gestation decreases
    - 23-26 weeks gestation as many as ~45% of women in labor have positive amniotic fluid cultures

• **Perinatal Infections**
  - Maternal infection and risk of preterm birth
    - ~25% of all preterm births associated with maternal infections
    - Risk of infection increases as gestation decreases
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• **Transplacental Perinatal Viral Infections**
  - May account for 5-10% of all cases of CP
    - **Toxoplasmosis**
      - 1:1,000 live births; 3,000 infants per year
      - Risk of seizures, MR and motor abnormalities ~ 75%
      - Antibiotic treatment reduces risk to ~ 30%
    - **CMV**
      - 1:1000 live births;
      - 90% of affected infants are asymptomatic at birth
      - 80-90% of symptomatic infants → neurologic injury
      - Chorioretinitis, microcephaly, sensorineural hearing loss
      - Most common viral infection associated with CP

  - **Herpes Simplex**
    - 1:5,000 – 26,000 live births
    - 400 to 1000 cases annually in US
    - Three distinct syndromes
      - Localized (skin, eye, mouth)
        - With treatment ND morbidity is very rare
      - CNS involvement
      - Disseminated disease
        - Microcephaly, porencephalic cysts, blindness, CP
        - ~ 50% of survivors demonstrate neurodevelopmental abnormalities
• Bacterial Vaginosis
  – Altered normal vaginal flora
  – BV seen in 20% of all pregnancies
  – Carries a 2-6 fold increase risk of preterm birth
  – Strong association with chorioamnionitis
    • ~ Responsible for 80,000 preterm births annually
    • ~4,000 infants → permanent neurologic disability

• Nongenital Tract Infections
  – UTI
  – Maternal periodontal disease (~18%)

• Neonatal Infections
  – Pneumonia
    • PPHN with severe hypoxemia
    • Arterial spasm, ↑ capillary permeability, coagulopathy
  – Meningitis
    • Inflammatory vasculitis → vessel obstruction
    • Bacteria invade brain → necrotizing lesions
    • Liquefaction, cavitation, progressive hydrocephalus
    • CP in 20-50% of survivors of meningitis
  – SIRS & MODS
    • Modulated by pro-inflammatory cytokines

• Intra-Amniotic Infections (IAI’s)
  – “Clinical Chorioamnionitis”
    • Occur in ~50% of preterm births < 30 wks EGA
    • Signs & symptoms include
      – Maternal fever, leukocytosis, fetal tachycardia, uterine tenderness, foul-smelling amniotic fluid
      – Histologic chorio evidenced in only 62% of cases
    • Strong association between IAI’s, preterm rupture of membranes, preterm birth
    • Mechanism
      – IAI’s initiate immune response → cytokines, prostaglandins
      – Cause cervical softening, ROM, contractions

• Prematurity + LBW + Infection/Inflammation

• “Dual Role of Inflammation”
  – Interplay between proinflammatory challenge
  – Indigeneous protective responses
    • Endotoxin release
    • Stimulates TLR
    • Signal transduction pathways
    • Induced gene expression
    • Release of inflammatory cytokines

• “Histologic Chorioamnionitis”
  – May or may not be associated with infection
  – ROM not a prerequisite
  – Few women with H. chorio → clinical findings
    • ? Suboptimal culture techniques
    • ? Fastidious organism – mycoplasma, ureaplasma
      • ? Intrapartum antibiotic therapy
    – Associated with preterm birth & risk of
      • IVH
      • Periventricular echodensities
      • NEC
      • CP

Tridakse & Rugolo. Neonrvews 2007;8;e522-e632

Mechanisms of Cellular Injury

- Cytokines
  - Diverse group of soluble proteins
  - Produced by multiple cells
  - Function as intracellular messengers
  - Operate by pleiotropy & redundancy
  - Both pro- and anti-inflammatory agents
    - Interleukins
    - Interferons
    - Tumor Necrosis Factor

IAI and Cytokine-Induced Damage

- Cytokines exert a direct toxic effect
  - ↑ Production of nitric oxide synthase, free radicals
  - Cytokines interrupt oligodendrocyte development
  - ↓ Myelination, white matter injury, PVL, CP
  - 4-6 fold increase risk for white matter damage
  - 88% of brain tissue in infants with PVL
  - 6 fold increase in CP in preterm infants with FIRS

IAI and Birth Asphyxia

- IAI most common antecedent to
  - Birth depression, low APGAR score, HIE
- Mechanisms
  - Placental dysfunction due to villous edema
  - Placental abruption
  - Increased oxygen consumption
  - Reduced uterine blood flow
  - Endotoxic effect

IAI + Birth Asphyxia → HIE

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Loss of Cellular Function

- Depletion of ATP Reserves
- Anaerobic Metabolism
- Depletion of Oxygen Delivery
- ATP Energy stores
- Loss of ion gate control: Intracellular H+ & Ca++, water
- Energy inefficient state
- Lactic acidosis
- Loss of CBF
- Depletion of Oxygen Delivery
Cellular Death

“Hypoxic-ischemic brain damage is an evolving process, which begins during the insult and extends into the recovery period after resuscitation.”

Vannucci & Perlman

Necrosis
- Occurs rapidly
- Characterized by cellular swelling, membrane breakdown, activation of phagocytosis

Apoptosis
- Occurs slowly over hours to days
- Characterized by cellular shrinkage, nuclear pyknosis, genomic fragmentation

Simplexity

- Why Simple Things Become Complex and How Complex Things Can Be Made Simple
  - Things that seem complicated can be astoundingly simple
  - Things that seem simple can be dizzyingly complex
  - The science of redefining how we look at the world and using that new view in our work and lives


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