CEREBRAL PALSY:
CAN WE PREVENT IT?

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FINANCIAL DISCLOSURES

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OUTLINE

1. WHAT IS CEREBRAL PALSY?
2. ETIOLOGY OF CEREBRAL PALSY
   A. EXAMPLES OF CAUSES
3. WHAT IS A BETTER TERM FOR CEREBRAL PALSY? NEONATAL ENCEPHALOPATHY?
4. HYPOXIC ISCHEMIC ENCEPHALOPATHY
5. ARE THESE SPECIFIC MARKERS FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY? WHAT IS AVAILABLE?
6. INTRAPARTRUM ASSESSMENT
   HAS THE FETAL MONITOR DECREASED THE INCIDENCE OF CEREBRAL PALSY AND IF NOT WHY?
7. CLINICAL FEATURES OF HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE)
8. LABORATORY FEATURES OF HIE
9. X-RAY FEATURES OF HIE
10. PATHOPHYSIOLOGY OF HIE
11. CURRENT TREATMENT OF HIE
12. FUTURE TREATMENT AND PREVENTION
DEFINITION OF CEREBRAL PALSY

- It is a static motor and/or intellectual deficit usually present at birth secondary to lack of oxygen and blood flow during the intra-partum or pre-partum period.
WHAT CAUSES DEPRESSED BABIES?
DEPRESSED BABIES

1. Muscle Disease
   A. Muscular Dystrophy
   B. Congenital Myopathies
   C. Myasthenia Gravis

2. Genetic Disease

3. Developmental Abnormalities of Brain, i.e.
   A. Ageneses of the Corpus Collosum
   B. Lissencephaly
   C. Polmicrogyria

4. Rupture of the Uterus

5. Placental Dysfunction

6. Fetal Maternal Transfusion

7. Abruption

8. Fetal Hydrops

9. Small for gestational age-intrauterine growth retardation

10. Cord Compression

11. Thrombophilia, i.e., Hypercoagulable States

12. Toxins, i.e., Cocaine, etc.

13. Infection, i.e., Bacterial Virus, The Fetal Inflammatory Response Syndrome
THEREFORE, WHAT IS THE BETTER TERM?

THE BETTER TERM IS NEONATAL ENCEPHALOPATHY MANIFESTED BY THE FOLLOWING THEN DEFINE WHAT IT IS DUE TO:

I. NEONATAL ENCEPHALOPATHY: THIS IS A NEUROLOGICAL SYNDROME WITH THE CLINICAL FEATURES CONSISTENT WITH A DISORDER OF THE BRAIN. THE MOST NOTABLE CLINICAL FEATURES ARE THE FOLLOWING:

A. DEPRESSION OF LEVEL OF CONSCIOUSNESS
B. THIS IS ASSOCIATED WITH RESPIRATORY DEPRESSION
C. ABNORMAL TONE AND STRENGTH
D. DISTURBANCE OF CRANIAL NERVE FUNCTION
E. ESPECIALLY FEEDING AND OFTEN TIMES ACCOMPANIED BY SEIZURES
WHAT ARE THE CAUSES OF NEONATAL ENCEPHALOPATHY?

1. HYPOXIC ISCHEMIC DISEASE
2. HYPERBILIRUBINEMIA
3. INTRACRANIAL HEMORRHAGE
4. METABOLIC DISORDERS
5. MITOCHONDRIAL DISORDERS
6. TRAUMATIC ENCEPHALOPATHY
7. EPILEPTIC ENCEPHALOPATHIES
8. NEURODEGENERATIVE DISORDERS, I.D. CANAVAN’S AND ALPERS
9. INFECTION
STAGING OF NEONATAL ENCEPHALOPATHY I.E. SARNAT CRITERIA
# STAGING

<table>
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<th>Grade I Mild</th>
<th>Grade II Moderate</th>
<th>Grade III Severe</th>
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<tr>
<td><strong>Alertness</strong></td>
<td>Hyperalert</td>
<td>Lethargy</td>
<td>Coma</td>
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<td><strong>Muscle tone</strong></td>
<td>Normal or increased</td>
<td>Hypotonic</td>
<td>Flaccid</td>
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<tr>
<td><strong>Seizures</strong></td>
<td>None</td>
<td>Frequent</td>
<td>Uncommon</td>
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<tr>
<td><strong>Pupils</strong></td>
<td>Dilated, reactive</td>
<td>Small, reactive</td>
<td>Variable, fixed</td>
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<tr>
<td><strong>Respiration</strong></td>
<td>Regular</td>
<td>Periodic</td>
<td>Apnea</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>&lt;24 Hours</td>
<td>2-14 Days</td>
<td>Weeks</td>
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ASPHYXIA

This term should be used only for definition. “Marked impairment of gas exchange leading, if prolonged, to progressive hypoxemia, hypercapnea and significant metabolic acidosis.” This term describes a process of varying severity and duration rather that an end point and should not be applied to birth events unless specific evidence of a markedly impaired intra partum or immediate post natal gas exchange can be linked to neurological illness in the neonate.
ARE THERE SPECIFIC MARKERS FOR HYPOXIC ISCHEMIC INSULTS PRIOR TO BIRTH IN UTERO?

NONE YET
USE OF THE FETAL MONITOR TO IMPROVE AND DIAGNOSE INTRAPARTRUM HYPOXIA ISCHEMIA

1. IT WAS INTRODUCED IN THE 1960’S
2. IT HAS NOT CHANGED THE INCIDENCE OF CEREBRAL PALSY IN FIFTY (50) YEARS. IT IS STILL 1 TO 3 PER THOUSAND
3. THE DIFFICULTY IS THE FALSE POSITIVE RATE IS 99%, I.E. CHANGES IN THE FETAL MONITOR SUCH AS DECREASE IN BEAT TO BEAT VARIABILITY, LATE DECELERATIONS, ETC.
4. SO, IF THE FETAL MONITOR IS ABNORMAL HAS THE PROBLEM ALREADY OCCURRED OR IS IT GOING TO OCCUR?
SO THEREFORE WHAT IS NEEDED IS SOME TYPE OF MARKER OR WHEN IN FACT WHAT ARE THE CHANGES IN THE FETAL MONITOR THAT YOU MAY BE SUSPICIOUS OF FETAL ACIDOSIS OR HYPOXIA? THE ONLY THING THAT IS AVAILABLE AT THIS TIME AND SHOULD BE EXPLORED IS BEDSIDE MRI WITH DIFFUSION WEIGHTED IMAGES AND SPECTROSCOPY ON THE PREGNANT WOMEN IN LABOR
WHAT IS THE BETTER TERM? WHAT ARE THE FEATURES THAT SHOULD BE PRESENT IF YOU ARE GOING TO DIAGNOSE HYPOXIC ISCHEMIC ENCEPHALOPATHY AT OR ABOUT THE TIME OF BIRTH WHICH WILL ULTIMATELY CAUSE CEREBRAL PALSY?

1. ARTERIAL UMBICAL CORD GAS CONSISTENT WITH METABOLIC ACIDOSIS, PH OF LESS THAN 7.0 WITH A BASE EXCESS OF GREATER THAN MINUS 12.
2. DEPRESSED APGAR SCORES, I.E. LESS THAN 3 AT 1/5/10 MINUTES
3. A NEONATAL ENCEPHALOPATHY
4. IMAGING STUDIES CONSISTENT WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY
LET’S TALK ABOUT THE CLINICAL, LABORATORY, AND RADIOLOGICAL FEATURES OF INTRAPARTUM HYPOXIC ISCHEMIC DISEASE
FOCAL AND MULTI FOCAL BRAIN INJURIES, CLINICAL EVALUATION AND CLINICAL SYMPTOMS:

A. BIRTH TO 12 HOURS
   1. DEEP STUPOR
   2. VENTILATORY DISTURBANCE WITH RESPIRATORY FAILURE
   3. INTACT PUPILARY RESPONSES
   4. INTACT OCULAR MOTOR RESPONSES
   5. HYPOTONIA
   6. SEIZURES

B. BIRTH TO 24 HOURS
   1. VARIABLE LEVEL OF ALTERNESS
   2. MORE SEIZURES
   3. APNEA
   4. JITTERNESS
   5. PARALYSIS

C. BIRTH TO 24 TO 72 HOURS
   1. CONTINUED STUPOR
   2. DISTURBANCE OF CRANIAL NERVE FUNCTION
   3. HYPOTONIA MOVING TO HYPERTONIA
   4. WEAKNESS IN THE PROXIMAL LIMBS, UPPER GREATER THAN LOWER
WHAT ARE THE LABORATORY FEATURES THAT HELP YOU TIME WHEN A HYPOXIC ISCHEMIC EPISODE OCCURRED PRIOR TO BIRTH?

1. Umbilical cord gas with an acidosis of less than 7.0, base excess minus 12 or less.
2. Increased nucleated red blood cell count (normal: equal to 10 or less)
3. Increased Creatinine (normal: less than 1.0)
4. Increased liver function studies (normal: sgot less than 70)
5. Low platelet count (normal: 200,000)
ARTERIAL CORD GASES

1. If normal, no acute asphyxial event.

2. Even if you have a significant acidosis with a pH of less than 7.0 and with a base excess of greater than minus 12, only 3% of babies with a pH of less than 7.0 have a permanent problem, 50 to 75% of these go on to a normal new born nursery.

3. So acidosis is not a real good marker except that there was some hypoxia present just prior to birth.
NUCLEATED RED BLOOD CELL COUNT

1. Normal is less than 10 in term infants.
2. Hypoxia inducible factor 2 alpha is stimulated by Hypoxia.
3. Hypoxia inducible factor 2 alpha stimulates erythropoietin or epo from the fetal liver and takes 4 hours.
4. Erythropoietin then stimulates the release of nucleated red blood cell count which takes 24 hours.
   o So one can mark 28 hours prior to obtaining a nucleated red blood cell count is when an insult could have occurred.
THE CONCEPT OF MULTI SYSTEM ORGAN INVOLVEMENT

- Creatinine
- SGOT, SGPT
WHAT ABOUT CREATININE AND LIVER FUNCTION STUDIES?

These are extremely important also. Remember that if babies have ischemic insults prior to birth that injuries the kidneys, there is a markedly elevated creatinine and impaired renal function. If it is normal and goes up significantly after birth, then the insult occurred at that particular point. If the creatinine is significantly elevated prior to birth or at the time of birth, it means the insult occurred prior to birth and may be several days prior to birth. It is the same issue with SGOT and SGPT. Babies with significantly elevated liver function studies at birth have had previous chronic insults and not an acute insult. If the levels are elevated and then go down, it tells you that the insult also occurred prior to birth.
WHAT ABOUT PLATELET COUNT?

STUDIES HAVE FOUND THAT BABIES WHO HAVE PRE-ADMISSION BRAIN DAMAGE, IN OTHER WORDS, PRE-PARTUM ARE SIGNIFICANTLY MORE LIKELY TO HAVE PLATELET COUNTS LESS THAN 100,000 WITHIN FIVE DAYS OF BIRTH.
WHAT ARE THE CAUSES OF CEREBRAL PALSY?
YOU MUST RELATE IT TO PREPARTUM, INTRAPARTRUM HYPOXIC ISCHEMIC ISSUES

1. ABRUPTION OF THE PLACENTA
2. PROLAPSE OF UMBILICAL CORD
3. HEMATOMA OF THE UMBILICAL CORD
4. ABNORMAL PLACENTA WITH VILLAMENTOUS INSERTION
5. INFECTION, I.E. GROUP B. STREPTOCOCCUS
6. RUPTURED UTERUS
7. COCAINE OR STIMULANT ABUSE
8. PLACENTAL INSUFFICIENCY, I.E. VARIOUS CAUSES
9. SYSTEMIC MATERNAL DISEASES
PLACENTA

1. IN ANY DEPRESSED BABY, THE PLACENTA SHOULD BE PRESERVED AND EXAMINED GROSSLY AND MICROSCOPICALLY
2. THIS EXAMINATION OFTEN MAY REVEAL THE ETIOLOGY OR THE CAUSE OF THE DEPRESSION OF THE INFANT
Figure 6-12. Uterus of pregnant woman showing normal placenta in situ. A. Location of section shown in Figure 6-13. B. Location of section shown in Figure 6-14.
Figure 21-4. Total placental abruption with concealed hemorrhage. The fetus is now dead.
Figure 23-1. Placenta demonstrating bilobed structure, marginal insertion of umbilical cord, and partial villous insertion of cord (fetal vessels traversing membranes to reach smaller placental lobe on right).

Figure 23-2. Cirrha (left) and marginate (right) varieties of extrachorial placentas.
Figure 23-19. A sharply localized stricture in a cord from a stillborn infant. (From Fox: Pathology of the Placenta. Philadelphia. Saunders. 1978, Volume 7, page 442.)

Figure 23-20. Hematoma of the umbilical cord.
MICROSCOPIC SLIDE OF CHORIOAMNIONITIS
MECHANISM OF INJURY DUE TO CHORIOAMNIONITIS

1. BACTERIA (ANTIGENS)
2. INFLAMMATION OF THE AMNION AND CHORION
3. PRODUCTION OF THE FETAL INFLAMMATORY RESPONSE SYNDROME I.E. CYTOKINES, TUMOR NECROSIS FACTOR, ETC.
4. ENTERS THE CENTRAL NERVOUS SYSTEM AND STIMULATES THE TOLL RECEPTORS PRODUCING FURTHER CYTOKINE PRODUCTION, GLUTAMATE, NITRIC OXIDE, FREE RADICALS.
5. THEN CAUSES VASCU LIS, HYPOXIA ISCHEMIA RESULTING IN A HYPOXIC ISCHEMIC ENCEPHALOPATHY
SO LET’S SUMMARIZE:

Acutely asphyxiated infants have cord gases with pH’s of less than 7 and a base excess of greater than minus 12, normal nucleated red blood cell count, normal creatinine, SGOT and normal platelet counts. Chronically asphyxiated infants have normal pH’s, increased nucleated red blood cell counts, increased creatinine and SGOT and declining platelet counts. Pretty good way to confirm your clinical suspicions.
LET’S TURN TO IMAGING STUDIES, WHAT DO WE SEE:

1. Ultrasound
2. CT Scan
3. MRI Scan
PATTERN OF INJURY BASED ON THE STUDIES OF RONALD MYERS, 1978 IN RHESUS MONKEYS THE FOLLOWING OCCURS:

1. Selective neuronal necrosis on the parasagittal or water shed of the cortex and subcortical white matter. It is bilateral and symmetrical. This is due to decreased intermittent perfusion of cerebral blood flow on a chronic basis.
Figure 8-7  Parasagittal cerebral injury, coronal view. Schematic diagram of the distribution of the injury, which is indicated by symmetrical black areas in the superomedial aspects of cerebrum.
Figure 8-9 Parasagittal cerebral injury, lateral view. Schematic diagram of cerebral convexity, lateral view, showing distribution of major cerebral arteries. The distribution of injury, shown by the line-marked area, is in the border zones and end fields of these arteries.
PARASAGITTAL CEREBRAL INJURY

Figure 8-8 Parasagittal cerebral injury. A. Coronal section of cerebrum in an asphyxiated, full-term infant who died on the third postnatal day. Areas of necrosis of cerebral cortex and subcortical white matter in the parasagittal regions are marked by arrowheads. B. Lateral view of cerebral convexity of a 6-month-old infant who had experienced severe perinatal asphyxia. Note the cortical atrophy in parasagittal distribution (compare with...
ACUTE ISCHEMIC INJURY TO THE BRAIN, THIS IS AGAIN BASED ON THE RONALD MYERS 1978 STUDIES IN RHESUS MONKEYS

1. The injury occurs in as little as 10 minutes. It usually does not exceed 25 minutes. In Myers study if the ischemic process exceeded 25 minutes the monkey died. This pattern of injury is quite different and involves the basal ganglia, thalamus, rolandic cortex, internal capsule and brain stem.
ACUTE ISCHEMIC INJURIES

Figure 8-3  Neuropathology of the deep nuclear-brain stem form of selective neuronal necrosis. A, Schematic depiction of the topography of the lesions in a typical case of a term newborn subjected to severe, terminal asphyxia. The dark areas indicate nuclei with neuronal loss, and the diagonally striped areas represent regions of marked gliosis. B, Holzer stain of the pons for gliosis in a typical case. The tegmentum is atrophied and deeply stained because of gliosis; the base of the pons is nearly normal. (From Natsume J, Watanabe K, Kuno K, Hayakawa F, et al: Clinical, neurophysiologic, and neuropathologic features of an infant with brain damage of total asphyxia type (Myers), Pediatr Neurol 13:61-64, 1995.)
FOCAL AND MULTI FOCAL BRAIN INJURIES

1. The third variety is less common, results from generally the blockage of a single vessel or abnormal development of a certain vessel and results in focal infarct, usually the middle cerebral artery, most common on the left side. Probably the most common etiology is a hyper coagulable state in the mother.
Figure 8-35  Focal Ischemic brain injury. Coronal section of the cerebrum from a full-term infant with thrombosis of the left middle cerebral artery and a large ischemic infarct. The infant died 2 days after birth complicated by meconium aspiration. (From Baranada MA, Moosy J, Shuman RM: Cerebral infarcts with arterial occlusion in neonates, Ann Neurol 6:495-502, 1979.)
1. We have talked about early identification by ante partum and intra partum assessment of the infant for highest risk for each evolving injury.

2. Based on the evaluation: what is needed is supportive care to facilitate adequate perfusion and nutrients to brain.

3. Finally, considerations of interventions to ameliorate the process of ongoing brain injury.
THE INJURY CASCADE

Although the cellular targets of HI are different depending on age and severity of insult, the basic cascade of injury occurs in a uniform way regardless of age and continues for a prolonged period of time. Cell death occurs in 2 main phases: primary death from hypoxia and energy depletion, followed by reperfusion and production with secondary energy failure and death. A tertiary phase was recently proposed, in which factors can worsen outcome, predispose a newborn to further injury or prevent repair or regeneration after an insult to the brain.
PATHOPHYSIOLOGICAL PROCESS LEADING TO DELAYED NEURONAL DEATH

1. Insults i.e. asphyxia, impaired perfusion
2. Primary neuronal death (necrosis)
3. Delayed neuronal death (apoptosis)

Opportunity for intervention
NECROSIS

1. Morphology: Cell swelling, dispersed intracellular chromatin; membrane fragmentation inflammation
2. DNA fragmentation characteristics: usually rapid
3. Insult characteristic: more severe than apoptosis
Necrosis

1. HYPOXIA ISCHEMIA
2. DECREASED ATP
3. FAILURE OF ATP DEPENDENT SODIUM/POTASSIUM PUMP
4. SODIUM INFLUX
5. CHLORIDE AND WATER INFLUX
6. CELL SWELLING/LYSIS
7. EARLY CELL DEATH (NECROSIS)
APOPTOSIS

1. Morphology: Cell Shrinkage; chromatin condensation; intact membranes; no inflammation
2. DNA fragmentation: Specific oligonucleosomal cleavage.
3. Temporal characteristics: slow; usually days
4. Insult characteristics: less severe than necrosis
RELATIONSHIP BETWEEN ENERGY DEPLETION AND CELL DEATH

1. Hypoxia Ischemia
2. Decreased ATP
3. Failure of ATP Dependent Sodium/Potassium*
4. Membrane Depolarization
5. Increased Glutamate Release
6. Increase in Intracellular Calcium and Nitrous Oxide Species
7. Produces Free Radicals
8. Cell Death or Apoptosis
TREATMENT

1. Supportive Care
2. Hypothermia
   A. Head cooling
   B. Body cooling
WHAT ARE THE SELECTION CRITERIA AND TREATMENT AT USA MEDICAL CENTER?
PROTOCOL FOR HYPOTHERMIA NEONATAL ISCHEMIC ENCEPHALOPATHY FOR INFANTS \( \geq 36 \) WEEKS G.A. AND LESS THAN 6 HOURS OF AGE

SELECTION OF PATIENTS

1. The “obvious” one:

   - Cord 1' hr ABG:
     - pH < 7.0
     - Bp \( \geq 16\) mm Hg
   - pH 7.01-7.15
     - Bp 10-15 mm Hg
   - No ABG

   - Acute perinatal event
     - @10': Apgar < 5 or IPPV

   - Moderate or Severe Encephalopathy
POTENTIAL MECHANISMS OF HYPOTHERMIC PROTECTION

1. Programed cell death: Hypothermia is associated with suppression of the caspase-3 hypoxia associated protein synthesis.

2. Secondary inflammation: Hypothermia suppress micro glial activation production of inflammatory cytokines and other neuro toxins

3. Abnormal glutamate receptor activation: hypothermia reduces adverse changes in the composition of the ampa receptor (AMPA) and suppresses epileptiform transients and abnormal receptor activation and the effects of this given protection.
WHAT ARE THE OUTCOMES WITH COOL CAP AND TOTAL BODY HYPERTERMIA?

NOT AS GOOD AS YOU WOULD LIKE. IN FACT, NOT VERY GREAT.
GENERAL OUTCOMES WITH COOL CAP AND TOTAL BODY HYPOTHERMIA

1. Mortality rate was 27% in the hypothermic group versus 44% in the controls (3 in each of these groups died after 18 months)

2. Severe disability was 41% versus 60% in the controls

3. Among the survivors:
   A. Intellectual quotient was less than 70 and occurred in 27% versus 30% of controls
   B. Cerebral palsy was present in 17% versus 29% of controls
   ✷ In all studies with severe encephalopathy did much worse as opposed to mild to moderate encephalopathy as defined by Sarnat system
SUMMARY

1. Asphyxia which is an alternation of blood gases associated with acidosis and increased $\text{PCO}_2$, neonatal encephalopathy and appropriate imaging studies i.e. hypoxic ischemic patterns.

2. Most hypoxic ischemic injuries occur during that intra partum period.

3. The pathophysiology is due to decrease in high energy source, production of excitatory neuro transmitters, nitrous oxide production, free radical production which ultimately destroys cells.

4. The hypoxic ischemic injury causes two main clinical and radiological presentations:
   A. Parasagittal Injury
   B. Acute Ischemic Injury
SUMMARY (CONTINUED)

5. Clinically they are depressed with multi system organ involvement, neonatal encephalopathy, requiring extensive support.

6. Finally, therapy with hypothermia is partially effective.
WHERE DO WE GO FROM HERE:

1. Develop better appropriate diagnosis prior to the event or during the event.
2. Develop medications that are specific and more protection during re-profuson phase.
3. Are there potential treatments beyond six hours of age?