Neonatal Syndrome

Multisystem Maladaptation

Hypoxic Ischemic Syndrome
Perinatal Asphyxia
Hypoxic Ischemic Asphyxial Syndrome
Neonatal Maladjustment Syndrome
Dummy Foals
Changes in Behavior
Neonatal Intensive Care
Hypoxic-Ischemic Syndrome

• Human Neonates - cerebral palsy
  • Prolonged Stage II
  • Lawsuits
  • Clinical studies on onset
    • Intranatal
    • Prenatal
    • Postnatal

• Experimental Studies
  • Hypoxic ischemic insults
  • Hypoxic ischemic encephalopathy (HIE)
Neonatal Problems
Hypoxic Ischemic Asphyxial Disease

- Selective neuronal pathology
- Renal pathology
- Gastrointestinal pathology
- Metabolic failure
- Cardiovascular pathology
- Endocrine abnormalities
- Pulmonary pathology
Neonatal Problems

• Hypoxic ischemic asphyxial disease?
  • Often no evidence
• Inflammatory placental disease
  • Strong correlation
• Role of inflammatory mediators?
  • Cytokines, local vasoactive mediators
  • Primary effect?
  • Secondary hypoxic ischemic insult?
Neonatal Encephalopathy

Hypoxic Ischemic Insults

Inflammatory Insults
Role of Placentitis

• Many neonatal diseases
  • Multiple etiologies
  • Disruption of fetal life
    • Predispose to neonatal disease
    • Origin of the neonatal disease

• Placentitis - untreated
  • Neonatal diseases
    • CNS, Renal, GI

• Placentitis - treated
  • Protects against neonatal diseases
Septic Encephalopathy

• **Fetal**
  - Neuroinflammation
  - FIRS (Fetal Inflammatory Response Syndrome)
    - Fetal placentitis

• **Maternal**
  - Maternal placentitis
  - SIRS
  - Focal maternal infections
Septic Encephalopathy

Systemic Response
FIRS

Inflammatory mediators

BBB

BBB leaky

Cytokine receptors

Neuroinflammation

CNS inflammatory response

Hypoxic Ischemic insult
Neuroinflammation

- Important in the pathogenesis of
  - Septic encephalopathy
  - Hypoxic ischemic encephalopathy

- Microglia cells are key
  - Up-regulation of proinflammatory cytokines
  - Up-regulation of trophic factors

- Can result in
  - Morphological alterations
  - Biochemical alterations
  - Functional alterations
Neuroinflammation

• Response depends on mix
  • Proinflammatory
  • Anti-inflammatory
  • Specific mediators

• Mild disease – often no morphologic changes
  • Motor
  • Perceptual, visual
  • Behavioral
  • Cognition
  • Excitatory responses

• Excitotoxicity
Neurosteroids

- Protect the brain during fetal life
- Responsible for the somnolence
- At birth
  - Removal of the placental
  - Levels drop rapidly
  - Fetus to “awake up”
Neurosteroids

• Allopregnanolone
  • Brain levels induced by
    • Inflammatory mediators
    • Hypoxic ischemic insults
  • Protect against neuroexcitatory toxicity
  • Marked anti-seizure actions
  • Raise seizure threshold
  • Induces somnolence
Neurosteroids

• Pregnenolone and pregnenolone sulphate
  • Placenta also secretes
  • Excitatory action in the brain
  • Cross the blood brain barrier
    • Normal – slow
    • Abnormal BBB – rapid transfer
    • Inflammation
    • Hypoxic ischemic insult
Neurosteroids

Placenta ➔ Substrates ➔ Allopregnanolone

Fetal CNS

Pregnenolone Sulphate

BBB

FIRS

Pregnenolone Sulphate
Neonatal Encephalopathy

- Hypoxic Ischemic
- FIRS
- Placentitis
- SIRS

BBB

- Neonatal Encephalopathy
- Excitatory
Neonatal Encephalopathy

Neonatal Encephalopathy

Hypoxic Ischemic
FIRS Placentitis SIRS

Pregnenolone Sulphate

Placenta

FIRS

SIRS

Neurosteroid Substrates

Allopregnanolone

Excitatory
Typical Clinical Course

• Born near normal behavior
• Initial signs – excitatory
  • Constant activity – wandering, not lie down
  • Hyper-responsiveness
  • Hypertonus
  • Culminating in tonic-clonic seizure-like behavior
• Onset of somnolent phase
  • Stress induced adrenal steroidogenesis
  • Neuroinflammation induces neurosteroids
  • Healing period
• Recovery
Typical Clinical Course

• Born seizure-like behavior
  • Less placental steroidogenesis
    • Lower levels protective neurosteroids
  • Inflammatory mediators
    • Induced blood brain barrier deficits
    • Allow sulfated neurosteroids into CNS

• With neonatal stress onset of somnolent phase
  • Stress induced adrenal steroidogenesis
  • Neuroinflammation induced CNS neurosteroids
  • Healing period
Changes in responsiveness
Changes in muscle tone
Changes in muscle tone
Changes in behavior
Brain stem damage
Seizure-like behavior
Terms
Generic Description of Signs

• Neonatal Encephalopathy (NE)
• Neonatal Gastroenteropathy (NG)
• Neonatal Nephropathy (NN)
• Neonatal Metabolic Maladaptation
• Neonatal Cardiovascular Maladaptation
Insult
- Acute vs Chronic
- Mild vs Severe
- Single vs Repeated

Organs affected
- CNS
- Renal
- GI
- CV

Fetal response
- Gestational age
- Preexisting state
- Compensation

Outcome
Intrauterine Challenge

- Indications at birth of intrauterine challenge:
  - Cr level
  - Hypochloremia
  - High PCV
  - High birth blood glucose
  - Persistently low birth blood glucose
  - Ca levels
  - Fibrinogen level
  - WBC
  - Low cortisol
  - Lactate level
Fetal foal floating in a sea of creatinine
“Pong”

Thoroughbred foal
Born: May 7 at 6 PM
Admitted: May 8 at 8:53 AM
15 hrs old
“Pog”
History

• Term birth to a multiparas mare
• Normal gestation
• Stage 1 - not observed
• Stage 2 - 10 minutes or less
• Stage 3 - 1 hour
• Assisted to stand after 1.5 hours
  • Nursed from the mare
“Pog” History

- Never vigorous
- Got up once during night
  - Only for short time
  - Did not nurse
- Bottle-fed 8 oz. of colostrum
- Referred for intensive care
  - Weak
  - Inability to stand
Admission Physical

- Marked oral, nasal, scleral, aural icterus
- Oral, nasal, scleral, aural injection
- Multiple oral petechia
- Marked lingual erythema
- Abdomen
  - Meconium in the right dorsal colon
  - Few borborygmi
  - Fetal/neonatal diarrhea
“Pog”
Admission Physical

- Cardiovascular
- Cold hooves, cold legs
- Very weak pulses
- Poor arterial fill, poor arterial tone
- Neurologic signs
- Somnolent with occasional struggling
- Struggling appeared meaningful
### Admission Laboratory Data

<table>
<thead>
<tr>
<th>Test</th>
<th>Admission</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>461 mg/dl</td>
<td>150 mg/dl</td>
</tr>
<tr>
<td>WBC</td>
<td>800 cells/ul</td>
<td>5-10,000</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>62% cells/ul</td>
<td>50-80%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>38% cells/ul</td>
<td>20-50%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6.46 mg/dl</td>
<td>2.5-4.0</td>
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<tr>
<td>Glucose</td>
<td>44 mg/dl</td>
<td>60 – 120</td>
</tr>
<tr>
<td>PCV</td>
<td>54%</td>
<td>30 – 45%</td>
</tr>
<tr>
<td>TPP</td>
<td>6.1 gm/dl</td>
<td>4.0 – 5.5</td>
</tr>
</tbody>
</table>
Admission Problems

• Weakness, somnolence
• Not nursing
• Lingual erythema
• Injection
• Petechia
• Icterus
• Poor perfusion

• Diarrhea
• ↓ WBC,
  ↑ fibrinogen
• ↑ PCV, ↑ TPP
• ↑ Creatinine
• Hypoxemia
• ↑ lactate
“Pog”
Major Problems

• Sepsis/Septic shock
• Neonatal Encephalopathy
• Neonatal Gastroenteropathy
Neonatal Encephalopathy

- Periods - bright and active
- Sudden onset of somnolence
  - Somnolence/periods of arousal
- Apparent facial paresis
  - Right ear moves slowly
- Generalized weakness
“Pong”
Neonatal Encephalopathy

• Periodic apnea
  • Up to 60 sec
  • With clustered breathing
• Inappropriate central tachypnea
• Apneusis (apneustic respiration)
• Hypercapnia
  • Without apnea
“Pog”
Neonatal Encephalopathy

• Seizure like activity
  • Opisthotonus, tonic/clonic marching activity
  • Minimal nystagmus
• Lingual erythema
• Moderate nasal septum hyperemia
• Hyperresponsive to stimuli
• No suckle or searching
Neonatal Encephalopathy
CNS Signs

- Most common and noticeable
  - Signs occur predictably - 90%

- Mild central insult
  - Multifocal lesions
  - Selective neuronal dysfunction
  - Slow maturation of coordination
Neonatal Encephalopathy
Signs of CNS disease

• Changes in responsiveness
• Changes in muscle tone
• Changes in behavior
• Signs of brain stem damage
• Seizure-like behavior
• Coma, death
Neonatal Encephalopathy
Signs of CNS disease

• Changes in responsiveness
  • Hyperesthesia
  • Hyperresponsiveness
  • Hyperexcitability
  • Hyporesponsiveness
• Periods of somnolence
• Unresponsiveness
Neonatal Encephalopathy

Signs of CNS disease

• Changes in muscle tone
  • Extensor tonus
  • Hypotonia
  • Neurogenic myotonia
  • Inability to protract legs
Neonatal Encephalopathy

Signs of CNS disease

- Changes in behavior
  - Loss of suckle response
  - Loss of tongue curl
  - Loss of tongue coordination
  - Disorientation especially relative to the udder
  - Aimless wandering
  - Blindness
  - Loss of affinity for the dam
  - Abnormal vocalization ("barker")
Changes in behavior
“Poog”
Neonatal Encephalopathy
Neonatal Encephalopathy
Signs of CNS disease

- Changes in respiratory patterns
  - Central tachypnea (midbrain)
  - Apneusis (pontine)
  - Apnea (> 20 seconds, midbrain)
  - Cluster breathing (high medullary)
  - Ataxic breathing (medulla)
  - Cheyne-Stokes breathing - very rare

Central hypercapnia
Central Respiratory Patterns

- **Cheyne-Stokes**
- **Central Hyperventilation**
- **Apneusis**
- **Cluster breathing**
- **Ataxic breathing**

From: Bradley: Neurology in Clinical Practice, 5th ed
Neonatal Encephalopathy
Signs of CNS disease

• Signs of brain stem damage
  • Loss of thermoregulatory control
  • Weakness
  • Anisicoria (3rd nerve, one side)
  • Pupillary dilation (midbrain)
  • Pinpoint pupils (pontine)
  • Hypotension
• Loss of consciousness (reticular formation)
  • Vestibular signs - circling, head tilt
• Facial nerve paresis
Neonatal Encephalopathy
Signs of CNS disease

• Seizure-like behavior (tonic/clonic generalized)
  • Marching type behavior (clonic, partial or gen)
  • Abnormal extensor tone (tonic, partial or gen)
  • Seizures

• Coma, death
Neonatal Encephalopathy Treatment

• Nutrition
  • Not nursing
  • Trophic feeding
  • Parenteral Nutrition

• Respiratory
  • Intranasal oxygen
  • Caffeine
  • Positive Pressure Ventilation

• Seizures
  • Phenobarbital
“Pong”
Neonatal Encephalopathy

• Hospital day 2
  • Seizures – resolved with phenobarbital therapy
  • Began ventilation

• Hospital day 3 – standing

• Hospital day 5 – nursing from bottle, more aware

• Hospital day 6 – off intranasal oxygen

• Hospital day 9 – nursing from mare
“Pong”
Neonatal Nephropathy

• Creatinine level slow to drop
  • Above normal until hospital day 11

• High fractional excretion of Na
  • As high as 2.18% - normal for neonatal foal <0.3%
  • Still > 1% at discharge (day 20)

• Development of significant edema
  • Persisted until day 6
Neonatal Nephropathy

• Second most common target - 45%
• Common disease states
  • Mild decrease GFR
  • Mild acute tubular necrosis
  • Mild tubular dysfunction
  • Maldistribution of renal blood flow
• Less common disease states
  • Severe acute tubular necrosis
  • Irreversible acute damage
  • Chronic renal disease
Neonatal Nephropathy

- Oliguria
- Anuria
- Edema formation
- Fluid overload
- Weight gain
- Persistently elevated Cr
- Birth Cr slow to drop
- Abnormal fraction excretions
- High amikacin trough levels
- Slow response to fluid challenges
“Pong”
Neonatal Gastroenteropathy

- Fetal/neonatal diarrhea
- Retained meconium
- Too much abdominal fill for not being fed
- Abnormal abdominal palpation
  - One loop of bowel thickened wall
- Day 7 began passing feces
  - Frequency > 24 hours
  - Enema dependent
- Day 17 resolved
Neonatal Gastroenteropathy

• Third most common target - 40%
  • Especially when metabolic demands (digestion) are superimposed on cardiopulmonary instability

• Predisposition to sepsis and SIRS
  • Translocation of bacteria through the GI tract
Neonatal Gastroenteropathy

- Dysphagia
- Colic
- Abdominal distension
- Gastric reflux
- Diarrhea
- Constipation
- Dietary intolerance
  - Milk replacer
  - Other specie’s milk
  - Frozen mare’s milk
  - Fresh mare’s milk
Neonatal Gastroenteropathy

• Mild indigestion
• Dysmotility
• Ileus
• Diapedesis of blood into the lumen
• Mucosal edema
• Epithelial necrosis
• Development of intussusceptions or structures
• Hemorrhagic gastritis or enteritis/colitis
• Pneumatosis intestinalis
Neonatal Gastroenteropathy
Neonatal Syndrome
Cardiovascular tract

- Less commonly affected – 10%
- Poorly responsive peripheral vasculature
  - To hypovolemic challenges
  - To endogenous/exogenous adrenergic agents
- Cardiac disease
  - Inappropriate bradycardia
  - Premature ventricular contractions
  - Supraventricular tachycardia
  - Ventricular tachycardia
- Persistent fetal circulation/PPH
- Cardiovascular collapse
  - Refractory hypotension
  - Cardiovascular shock
  - Septic shock
“Pong”
Metabolic Maladaptation

• Hypoglycemia at admission – 44 mg/dl
• Hyperglycemic on glucose infusion – 243 mg/dl
  • Glucose diuresis
  • Hyponatremia, hypochloremia, hypokalemia
    • Diuresis, plasma osmotic effects
• Insulin therapy
  • Constant infusion regular insulin IV
  • Begun hospital day 2, weaned day 4
Neonatal Metabolic Maladaptation

Signs of Metabolic Disease

- Hypoglycemia
- Hyperglycemia
- Hypocalcemia
- Hypercalcemia
- Hyperlipemia/hyperlipidemia
- Slow response
  - To changing metabolic demands
Neonatal Syndrome

- NE - *Neonatal Encephalopathy*
- NN - *Neonatal Nephropathy*
- NG - *Neonatal Gastroenteropathy*
- NMM - *Neonatal Metabolic Maladaptation*
- NCM - *Neonatal Cardiovascular Maladaptation*
- NAM - *Neonatal Autonomic Maladaptation*
- NEM - *Neonatal Endocrine Maladaptation*
Problems

• Sepsis
  • Bacteremia - *Pantoea agglomerans*
• Septic shock
• Neonatal Encephalopathy
  • Central Respiratory failure – ventilation therapy
• Neonatal Nephropathy
• Neonatal Gastroenteropathy
Problems

- Neonatal Metabolic Maladaptation
- Edema
- Urachitis
- Hepatomegaly
- LDN
- Patent Urachus
- Over at knees
Therapeutic Interventions in Neonates
Neonatal Syndrome
Clinical Course/Therapeutic Intervention

• As severe organ dysfunction develops
  • Oxygen delivery to the tissues interrupted
  • Progression of more severe disease

• Therapeutic intervention
  • Prevent hypoxic ischemic episodes
  • Support organ system function
    • Allow recovery
  • Prevent secondary sepsis
  • Prevent other complications
Neonatal Syndrome
Maintain Tissue Perfusion/Oxygen Delivery

- Adequate cardiac output/perfusion
  - No magic blood pressure value
  - Adequate perfusion reflected by
    - Maintaining urine output
    - Perfusion of the limbs
    - Perfusion of the brain - mental status
    - Perfusion of bowel - GI function
- Inotrope and pressor therapy
Neonatal Syndrome
Maintain Nutrition

• Avoid
  • Catabolic state
  • Hypoglycemia
    • Hypermetabolism
• All compromised neonates
  • Will benefit from glucose therapy
• Hyperglycemia
  • Insulin therapy
• Enteral Nutrition
• Parenteral Nutrition
NE Therapy

• Support cerebral perfusion
  • Insure volemia
    • Careful fluid replacement
  • Defend perfusion
    • Inopressor therapy

• Insure oxygen delivery
  • Achieve pulmonary O₂ loading
  • Avoid anemia

• Nutritional support
  • Permissive underfeeding
Therapy

- DMSO
- Mannitol
- Thiamine
- MgSO4
- Others
Seizure Control

Phenobarbital?  Midazolam?  Others?
Neonatal Nephropathy
Therapy for Renal Dysfunction

• Avoid fluid overload
  • Ventral edema
    • Between front legs ("jelly belly")
    • Proximal limbs
    • Back
    • Generalized
  • Monitor body weight at least SID
    • Avoid NSAIDs
Neonatal Nephropathy
Therapy for Renal Dysfunction

Fluid restriction

• Most important management tool
• Deliver maintenance fluids or less
  • “Run them dry”
  • Balance nutritional needs/fluid overload
• Watch for onset of diuresis
  • Transition to high output renal failure
  • Initiation of normal renal function
Neonatal Gastroenteropathy
Treatment of GI Dysfunction

• Signs of damage lag behind other tissues

• Continued feeding with episodes of hypoxemia
  • May result in further damage
  • Oral feeding undertaken with great care
  • Full nutritional requirements cannot be met enterally
  • Partial parenteral nutrition
Neonatal Gastroenteropathy
Treatment of GI Dysfunction

• Important trophic substances in colostrum
  • Only small amounts needed for effect
• Luminal nutrition important to enterocyte health
  • Not feeding increases likelihood of translocation
• Small feedings 1-2 oz QID
  • Fresh colostrum - not refrigerated - best
  • Fresh mare’s milk
  • Frozen colostrum or mare’s milk
  • Don’t use milk replacer
Neonatal Syndrome
Recognition/Early Treatment of Secondary Infections

• Very susceptible to infections
• Monitor
  • For localizing signs of infection
  • Repeated blood cultures
• Repeat measurements of IgG
  • Repeated plasma transfusions
Therapeutic interventions

- INO2
- Fluid boluses
- Dobutamine
- Ticarcillin, clavulanic acid
- Plasma transfusion
- CRI glucose fluids
- Insulin
- Phenobarbital
- Caffeine
- Positive pressure ventilation
- Parenteral Nutrition
- Trophic feedings
- Sucralfate
- Domperidone -- mare
- TMS, Cephalexin
- Bandaging