High Risk Obstetrics:
Management, Tests, Technologies
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Learning Objectives:
Review the following screening tests performed during pregnancy:
1. Serum screening tests that may identify fetuses at risk for neurologic injury.
2. Ultrasound and serum screening for genetic disorders
3. Indications for fetal MRI and the potential for improving diagnosis and management
4. Serum biomarkers as a screening tool for neonatal hypoxic-ischemic encephalopathy to improve diagnosis, monitor the effect of therapy and improve prognosis.

Screening During Pregnancy
Routine
- Syphilis
- Gonorrhea
- Chlamydia
- Rubella
- Urine culture
- Cell Blood Count

Not Routine
- Cytomegalovirus
- Toxoplasmosis
- Varicella
- Parvovirus

Cytomegalovirus in Pregnancy
- Microcephaly
- Ventriculomegaly
- Intracerebral calcifications

Toxoplasmosis in Pregnancy
1. Intracerebral calcification
2. Chorioretinitis
3. Hydrocephaly
4. Microcephaly
5. Convulsions
6. Mental retardation

Diabetes Screening in Pregnancy
- Screen at initial prenatal visit if diabetes in prior pregnancy or obesity
- Repeat screening at 26-28 weeks
- Insulin is considered 1st line treatment in pregnancy
- Oral hypoglycemic (metformin, glyburide) cross the placenta with levels that can be as high as maternal concentrations. The long term effect on the fetus is unknown, but a 2016 study showed similar neurodevelopmental outcomes at 2 years.

Routine Genetic Screening in Pregnancy
- Cystic Fibrosis
- Hemoglobinopathies
- Spinal Muscular Atrophy

Screening for Chromosomal Abnormalities
Screening for Chromosomal Abnormalities
- 1st Trimester Screen
- 2nd Trimester Screen
Screening for Genetic Abnormalities

- Cell free fetal DNA
  - Originates from trophoblasts making up the placenta
  - Fetal DNA is fragmented and makes its way into the maternal bloodstream via shedding of the placental microparticles
  - Observed as early as 7 weeks
  - cffDNA fragments are significantly smaller than the maternal DNA fragments in the bloodstream
  - Can be used for whole genome sequencing

Fetal Anatomical Survey

- Performed at ~ 20 weeks gestation

Fetal Echocardiogram

- Performed at ~ 22 weeks gestation in patients with a risk factor

Maternal Risk Factors

- Diabetes
- Anticonvulsant intake
- Previous child with CHD
- Infections: Parvovirus, Rubella
- Autoimmune Dz: SLE + Rho Ab

Fetal Risk Factors

- ↑ Nuchal thickness
- Abnormal ductus venosus
- Abnormal fetal cardiac screening
- Major extracardiac anomaly
- Abnormal fetal karyotype
- Hydrops
- Fetal dysrhythmia

Doppler Ultrasound

Can be used to assess blood flow in the:
1. Umbilical artery
2. Fetal middle cerebral artery (replaced service for Rh isoimmunization)
3. Fetal ductus venosus
4. Maternal uterine artery

Fetal MRI

- Image acquisition in < 1 sec which decreases motion artifact
- Ultrasound is the screening modality of choice
- Does not use ionizing radiation
- Children exposed to MRI as fetus do not have disability at 3 yrs
- Avoid gadolinium based MR contrast agents
- Imaging can be performed outside the axial, coronal and sagittal planes without the near-field attenuation caused by the fetal skull during ultrasound
- May change diagnosis and affect management in up to half of cases with suspected cerebral anomaly

Indications for Fetal MRI

- Brain & Spine
  - Ventricleomegaly
  - Agenesis of the corpus callosum
  - Holoprosencephaly
  - Renal tract abnormalities
  - Cerebral cortical malformations
  - Vascular malformations
  - Infarctions
  - Neural tube defects
  - Sacrococcygeal teratoma
  - Caudal regression sequence
  - Craniofacial anomalies

Electronic Fetal Heart Rate Monitoring

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<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<td>0.72</td>
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<td>94.9%</td>
<td>69.2%</td>
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<tr>
<td>Debt 60</td>
<td>0.64</td>
<td>30.1%</td>
<td>91.0%</td>
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Based on pooled data from Sweden, Australia, Canada, Scotland, Denmark, England, U.S., Norway & Ireland

CP Prevalence & Cesarean Rates in Developed Countries

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<thead>
<tr>
<th>Country</th>
<th>CP Prevalence</th>
<th>Cesarean Rate</th>
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<tbody>
<tr>
<td>Sweden</td>
<td>0.15</td>
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<tr>
<td>Denmark</td>
<td>0.19</td>
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<td>U.S.</td>
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<tr>
<td>Norway</td>
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</tr>
<tr>
<td>Ireland</td>
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<td>36.0%</td>
</tr>
</tbody>
</table>

Umbilical Artery Gases

Frequency distribution of umbilical artery blood pH to babies with Apgar scores 1 min birth

8/21/2017
Neonatal Encephalopathy & Neurologic Outcomes, ACOG 2014

II. Neonatal Signs Consistent with an Acute Peripartum or Intrapartum Event

A. Apgar < 5 at five and ten minutes
   1. Clearly confer a relative risk of CP; however, most won’t develop CP.
   2. If Apgar > 7 at five minutes unlikely peripartum hypoxia-ischemia played a role in causing neonatal encephalopathy

B. Fetal Umbilical Artery Acidemia
   1. If pH < 7.0 or BD > 12 mM probability NE had an intrapartum hypoxic component
   2. If pH > 7.2 unlikely that intrapartum hypoxia played a role in causing NE

C. Neuroimaging evidence of acute brain injury seen on brain MRI or MR spectroscopy c/w Hypoxia-ischemia

D. Presence of multisystem organ failure c/w HIE

Neonatal Encephalopathy & Neurologic Outcomes, ACOG 2014

III. Type and timing of contributing factors that are c/w an acute peripartum or intrapartum event

A. Sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery
   Ex: ruptured uterus, abruption, cord prolapse, amniotic fluid embolism, Maternal CV collapse, vasa previa, massive fetomaternal hemorrhage

B. FHR monitor patterns c/w an acute peripartum or intrapartum event

C. Timing and type of brain injury patterns based on imaging studies c/w an etiology of an acute peripartum or intrapartum event

D. No evidence of other proximal or distal factors that could be contributing factors

IV. Developmental outcome is spastic quadriplegia or dyskinetic CP

Experimental therapies to treat Neonatal HIE

1. Head or Total body cooling
2. Erythropoietin
3. Allopurinol
4. Melatonin
5. Deferoxamine
6. New anticonvulsants
7. Intracerebral injection of neural stem/progenitor cells

Conclusions

• Although cytomegalovirus, toxoplasmosis and parvovirus are known to cause neurological morbidity and mortality they are not routinely screened for during pregnancy. We do not have effective therapy for congenital cytomegalovirus. We do have effective therapy for toxoplasmosis and parvovirus but they are so rare that routine screening is not cost effective.

• The fetus can be screened for chromosomal abnormalities in the 1st trimester. Screening with cell free fetal DNA will make invasive procedures such as chorionic villus sampling and amniocentesis obsolete.

• Fetal ultrasound, echocardiogram and MRI can be used to diagnose neurologic abnormalities and improve management.

• Neonatal serum biomarkers may improve our ability to diagnose hypoxic-ischemic encephalopathy, monitor the effect of therapy and improve prognosis.

References

• American College of Obstetricians & Gynecologists. Committee Opinion, Number 640, September 2015. Cell-free DNA Screening for Fetal Aneuploidy
• American College of Obstetricians & Gynecologists. Practice Bulletin, Number 151, June 2015. Cytomegalovirus, Parvovirus B19, Varicella Zoster and Toxoplasmosis in Pregnancy
• American College of Obstetricians & Gynecologists. Practice Bulletin, Number 133, July 2013. Ultrasound in Pregnancy
• American College of Obstetricians & Gynecologists. Practice Bulletin, Number 115, December 2010. Gestational Diabetes Mellitus
• American College of Obstetricians & Gynecologists. Practice Bulletin, Number 175, December 2016. Ultrasound in Pregnancy

• American College of Obstetricians & Gynecologists. Committee Opinion, Number 640, September 2015.

• Creasy & Resnik’s Maternal-Fetal Medicine, 7th edition, RK Creasy et al editors. 2014.
Prenatal Infections
From Rubella to Zika, Old Stories and New Concerns

Eliza Gordon-Lipkin, MD
August 3, 2017
lipkin@kennedykrieger.org

Case:
“I am a nurse and I am exposed to lots of sick people at the hospital. Do you think an infection while I was pregnant caused Joey’s developmental disability?”

Objectives:
1. To review the HISTORY of 3 major congenital infections.
2. To understand PATHOPHYSIOLOGY & impact on development.
   - The “bugs, genes, brains” relationship
   - Primary Mechanisms: Specific pathogens
   - Secondary Mechanisms: Inflammatory Cascade
3. To understand the approach to DIAGNOSIS & INTERVENTION for children with developmental disabilities.

Prenatal Infections: Why talk about them?
- Major cause of developmental disabilities
- Intellectual disability, Hearing impairment, Vision impairment, Cerebral Palsy, Autism?
- Growing number to consider beyond TORCH:
  - Toxoplasmosis, Syphilis, Rubella, Congenital CMV, & Varicella
  - Emerging understanding of influence on brain development.

Prenatal Infections Associated with Neurodevelopmental Disabilities:
- Toxoplasmosis
- Syphilis
- Varicella
- Parvovirus B19
- Rubella
- Congenital CMV
- Herpes Simplex Infection
- Congential lymphocytic Choriomeningitis Syndrome
- HIV
- West Nile Virus
- Chikungunya
- Congenital syphilis
- Hepatitis
- Zika Virus
- And more...

Congenital Rubella Syndrome:
- 1941 Sir Norman Gregg
- 1962-65 20k Infants born w/ CRS
- Microcephaly and a spectrum of developmental disabilities.
- Periods of vulnerability during gestation: timing of infection determines outcome.

Congenital Cytomegalovirus (CMV):
- 1956 JAMA
- 1968 Rubella Vaccine
- 1969 Rubella cases in US: 1969
- Now <1 case CRS/year in USA
- No cure, Low cost

Congenital Lubella Syndrome:
- 1962-65 20k Infants born w/ CRS
- Microcephaly and a spectrum of developmental disabilities.
- Periods of vulnerability during gestation: timing of infection determines outcome.

Images courtesy of cdc.gov
Cytomegalovirus (CMV):

- Most common congenital infection!
  - Incidence 0.2-0.7% of live births in USA (CDC)
  - Typically asymptomatic in immunocompetent adults.
  - Mean age of seroconversion: 28 yrs (Calugnati BMC ID 2007)
- Primary* exposure during pregnancy may manifest as:
  - Immediately evident at birth: Microcephaly, Palate anomalies, Hepatosplenomegaly, Hydrops
  - Evident after investigation: Sensorineural hearing loss, Retinitis, Intracranial calcifications
  - Evident long-term: Cerebral Palsy, Intellectual Disability, Late onset SNHL, Epilepsy

- Symptomatic at birth (10%): 50-75% will have long-term neurodevelopmental disabilities.
- Asymptomatic at birth (90%): 15-25% will have sensorineural hearing loss.
  Normal intelligent but “at risk” for learning disabilities.

Congenital Zika Virus Syndrome:

- ZIKV Infection: Fever, Rash, Conjunctivitis; 80% Asymptomatic
- Vulnerability: there is some suggestion that 1st trimester carries greater risk.
  1st Trimester 8-15% -- 2nd Trimester 5% -- 3rd Trimester 4% -- Overall 5-10%

- Prenatal Infections Associated with Neurodevelopmental Disabilities:
  - Toxoplasmosis
  - Syphilis
  - Varicella
  - Parvovirus B19
  - Rubella
  - Cytomegalovirus (CMV)
  - Herpes Simplex Infection
  - Congenital Lymphocytic Choriomeningitis Syndrome
  - HIV
  - West Nile Virus
  - Chikungunya
  - Consacale virus
  - Hepatitis
  - Zika Virus
  - And more...

Pathophysiology of Prenatal Infections

- Primary
  - Direct effects of pathogen on the developing fetus.

- Secondary
  - Effects of the maternal inflammatory cascade on fetal development.

Pathophysiology: Zika Virus


- Pathophysiology: Zika Virus

- Pathophysiology: Zika Virus

- Pathophysiology: Zika Virus

- Pathophysiology: Zika Virus
Infection triggers centrosome disruption → premature differentiation of neural progenitor cells → progenitor depletion → cortical thinning.

ZIKV infection affects the topology of human RNA

Maternal fever during 2nd trimester of pregnancy associated with 40% increased risk of child with autism.

None of the women who used ibuprofen to treat a fever during pregnancy gave birth to children later diagnosed with autism.

Mechanism: Maternal infection causes the release of inflammatory cytokines which has been found to alter the balance between pro-inflammatory and anti-inflammatory genes, leading to changes in brain development.

Evidence: Maternal infection and subsequent increase in inflammatory cytokines is associated with changes in expression of specific genes implicated in brain development.

Case:

"Can Joey be tested?"

"If it was an infection, what can be done?"

Antenatally

- Screening for some infections
- Clinical history
- Serologies, Amniocentesis
- Signs on ultrasound

Within 1st 3 wks of life

- "TORCH" workup (VGA, PCR, culture)
- Placental pathology/PCR when available

Within 1st year of life

- Serologies may be helpful (e.g. Rubella)
- Can exclude a diagnosis with negative IgG (e.g. CMV)

After 1st year of life

- No definitive diagnostic method
- May obtain stored sample retrospectively

Diagnosis: Mimickers

Consider the differential diagnosis of specific findings (e.g. microcephaly, congenital hearing loss, hydrops, etc.)

Radiographic mimickers of congenital infections:

- Aicardi-Goutières syndrome
- COL2A1 Mut
- COL4A1 Mut
- Juvenile Alexander Disease
- Cockayne Syndrome
- Krabbe, etc.

Diagnosis: How do we diagnose postnatally?

10% of children with CP had CMV DNA detected from Newborn Screen Cards

Consider the differential diagnosis of specific findings (e.g. microcephaly, congenital hearing loss, hydrops, etc.)

Radiographic mimickers of congenital infections:

- Aicardi-Goutières syndrome
- COL2A1 Mut
- COL4A1 Mut
- Juvenile Alexander Disease
- Cockayne Syndrome
- Krabbe, etc.
Prenatal infections are an important cause of developmental disabilities. Some specific infections should be considered in etiologic workup.

- Infection during pregnancy may affect the developing fetal brain by direct effects from the pathogen, as a result of a maternal immune and inflammatory response on fetal organ systems or fetal genome.

- Diagnosis after the neonatal period is difficult.

- Emerging research will investigate whether treatment after birth improves outcomes.

- Newborn screening for congenital CMV is an active area for research and debate with public health relevance in the near future.

**Intervention:**

- Vaccines for TORCH Mimickers
- Newborn screening
- Pre- and postnatal treatment
- Universal screening
- Targeted Approach
- Surveillance

**Intervention: How do we treat postnatally?**

2010: Oral valganciclovir in symptomatic infants x 6 months improves hearing outcomes at 12, 24 months and developmental outcomes at 24 months (language).

**References:**

- Banik A, Kandilya D, Ramya S, Stünkel W, Chong YS, Dheen ST. Maternal infection during pregnancy may affect the developing fetal brain by direct effects from the pathogen, as a result of a maternal immune and inflammatory response on fetal organ systems or fetal genome. Dev Med Child Neurol. 2017;59(7):784–790.


- Miller E, Cradock-Young S, Raynes-Germain RL. Outcomes at 24 months (language).


Adverse Childhood Events and Toxic Stress

American Academy for Cerebral Palsy and Developmental Medicine
Environmental and Genomic Factors in Neurodevelopmental Disabilities
Montreal, September 13 2017

Anna Maria Wilms Floet M.D., FAAP
Developmental/Behavioral Pediatrician
Kennedy Krieger Institute

No disclosures

At the conclusion of the talk, the participant should be able to:

• List a major finding from the ACE study and an implication for pediatric practice today
• Describe the concept of “toxic stress”
• Describe allostatic load in the context of a stress response

Basic Science of Pediatrics

Has the world gone “epidemic”? semantics of genetics

Epigenetics

Pediatrics Research
Next 7 great achievements?

3. Genomic discoveries predict, prevent, and more effectively treat disease
4. Big data recognize fetal and childhood origins of adult health and disease, resulting in effective intervention
5. Knowledge of the interaction of biology and the physical and social environment leads to effective prevention for individual and population health

Cheng et al, Pediatrics May 2017
New role for pediatricians in PREVENTION

Epigenetics?

Pediatrics
Barton Childs: 1999
Genetic medicine: A logic of disease
"...in the 21st century medicine will be directed towards treating individuals, not diseases. Health will be defined as a function of gene-environment homeostasis"

George Dover: 2009
Barker hypothesis and the relevance for pediatricians in diagnosis and prevent common adult-onset diseases

Epigenetics

Basic Science of Pediatrics

Has the world gone “epidemic”? semantics of genetics

Epigenetics
Johns Hopkins University medical student curriculum:

"...a new model of health and disease based on the principles of adaptation to the environment, variability of the genotype and stratification of risk, rather than simply a dichotomous view of "normal human biology (health)" and "abnormal physiology (disease)."

http://www.hopkinsmedicine.org/som/curriculum/genes_to_society/curriculum

Barton Child Rounds TODAY: Why this particular child? Why these findings? This disease? Why now? What could we have done and can do going forward to prevent or lessen the problem?

ACE study


CDC & Kaiser Permanente –1998
>17,000 white middle-income Americans
1995-1997 survey (retrospective)

Adverse Childhood Experiences (ACEs) contribute to negative lifetime physical and mental health morbidity and early mortality and affect > 60% of adults, in a dose-dependent manner

http://www.cdc.gov/ace/prevalence.htm

ACES Studies

Revision of the list of 10 ACEs used in the original study (Marie Mitchell 2013, Finkelhor 2015) for use in current pediatric populations

Evaluation of outcomes at different (childhood-young adult) ages (Kerker 2015, Jimenez 2016)

Clinical risk factors abuse

- Children younger than 4
- Special needs that may increase caregiver burden (e.g. disability, mental health, chronic physical health)

Risk factors for perpetration

- Parental "lack of understanding of children's needs, child development and parenting skills"
- Parental history of child maltreatment in family of origin
- Substance abuse and/or mental health issues in the family
- Parental characteristics (young age, low education, single parenthood, large number of dependent children, low income)
- Non-biological, transient caregivers in the home
- Parental thoughts and emotions that tend to support or justify maltreatment

Protective factors use

- Supportive family environment and social networks
  - Family Protective Factors
  - Stable family relationships
  - Household rules and child monitoring
  - Parental employment
  - Adequate housing
  - Access to healthcare and social services
  - Caring adults outside the family who can serve as role models or mentors

Community Protective Factors

- Communities that support parents and take responsibility for preventing abuse

Gene x Environment Interactions

differential susceptibility to context

ACE

But:
Many adults with high ACE scores were able to avoid negative outcomes
Not all children raised in privileged conditions do well

Questions:
1. What explains the individual variability in response to childhood adversity?
2. How do events in childhood become biologically embedded and affect outcomes like behavior, physical and mental health decades later?
Models for linkage ACES and later outcome

Diathesis stress model:
some children have a genetic predisposition/vulnerability to do poorly when faced with adversity (compared to their non-predisposed peers)

Differential susceptibility to context model:
some children are genetically more predisposed or reactive to their environment, others are less sensitive/swayed by their environment

The biology of stress

Differential stress model:
some children have a genetic predisposition/vulnerability to do poorly when faced with adversity (compared to their non-predisposed peers)

Differential susceptibility to context model:
some children are genetically more predisposed or reactive to their environment, others are less sensitive/swayed by their environment

Toxic stress

http://developingchild.harvard.edu/science/key-concepts/toxic-stress/

Allostatic load

• Cumulative "wear and tear" on the body that results from repeated cycles of adaptation

• Mechanism through which poverty and social disadvantage creates health disparities over the life course

Measures of allostatic load

• Epigenetic changes:
  – which genes are turned on when during development and where in the body
  – some epigenetic switches are dynamic (turned off/on in hours)
  – some are programmed early in life and remain stable across the life span
  – some may be passed on to the next generation

• Plasticity:
  – alteration in connectivity between amygdala, hippocampus and prefrontal cortex

Response to stress

Response to stress

Source: Mc Ewen, 1998

Pediatrics

AAP 2012

AAP 2012
**Pediatrics**
Biology of adversity
Review papers: Johnson SB et al
Science of Early Life Toxic Stress for Pediatric Practice and Advocacy - *Peds* 2013
State of the Art Review: Poverty and the Developing Brain - *Peds* 2015

**Outcome variable: words**

**Outcome variable: brain volume**

**Outcome variable: epigenetic markers?**

**Key points**
1. The foundations of lifelong health are built in early childhood
2. Advances in a broad range of fields, are converging on an integrated, basic science of pediatrics
3. From genes to society

**Next steps/frontiers**
Bernard Dan, DMCN 2012
Bernard Dan, DMCN 2017

**Next steps/frontiers**
CRISPR-Cas 9
How Are We Integrating Basic Knowledge Into Clinical Practice?

- Glutamate-mediated excitotoxicity triggers CP through a cascade of injury that can be treated clinically with therapeutic hypothermia and reduced with magnesium sulfate in fetuses with threatened pre-term labor.

- Inflammation is a second major mechanism for CP triggered by hypoxia-ischemia and infection, and pre-clinical evidence suggests that it's severity can be reduced by nanoparticle-delivered anti-inflammatory agents and cell-based therapies.

- Neurogenetic and epigenetic mechanisms for disabilities may also trigger these two major mechanisms, leading to therapies for these disorders as well.

NMDA Channel Blocker MK-801 Prevents Damage from HIE or Direct Injection of NMDA

However, the therapeutic window is short.

The Excitatory Glutamate Synapse and NMDA Receptors are Critical for Initiating the Hypoxic-Ischemic Cascade of Injury

HIE Impairs Glutamate Pumping Out of the Synapse Leading to Extrasympathetic Flooding


CSF Glutamate Correlates with Severity of Neonatal Encephalopathy


Figure 1

Near-Total Asphyxia Damages Regions Connected by Glutamate Pathways and Causes Dyskinetic CP

The HIE insult is global but the injury is usually focal.

T2 Weighted MRI

The HE insult is global but the injury is usually focal.

Brain Section
Asphyxia Damages Structures Connected by Excitatory Pathways

Excitotoxicity Activates NMDA Receptors and nNOS Which Is Toxic To Mitochondria and Causes Delayed Cell Death

Glutamate → NMDA + Ca

Mitochondrial Damage → NO → Cell Death

nNOS = neuronal nitric oxide synthase; NO = nitric oxide

The severity of NMDA mediated brain injury is dependent on brain temperature in the immature rat pup. (McDonald et al, Neuroscience Lett 1991)


Thoresen et al, Post-hypoxic hypothermia reduces cerebrocortical release of NO and excitotoxins, Neuroreport, 1997.


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Neuronal Hyperactivity Stimulates Microglial Activation Via Neuronal NMDA Receptors

Eyo et al., J Neuroscience 2014;34:10528-10540.

Microglial NMDA receptors also drive inflammation (Kaindl et al., 2012).

Can Mg++ Sulfate Reduce the Risk of CP in Very Low Birthweight Infants?

Karin B. Nelson and Judith K. Grether

Pediatrics 95:263-269, 1995

Mg++ Reduces NMDA Mediated Brain Injury in Neonatal Rats

Mg++ Before Early Preterm Delivery Reduces Rate of CP

Numerous Clinical Trials Confirm Protective Effects of Magnesium Sulfate for CP Associated with Premature Labor:

American College of Obstetricians and Gynecologists, 2010 and 2016:

The available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfates for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concomitant tocolysis, and monitoring in accordance with one of the larger trials.

Nanomedicine for Brain Injury

Summary

• Postnatal therapy for prenatal injury
• Targeted therapy can prevent or arrest fetal neuroinflammation
• Platform for delivering drugs in a targeted, sustained manner for brain injury: implications in other neurodegenerative diseases

Dendrimer rapidly co-localizes in activated microglia in the periventricular region in rabbits with CP

Dendrimer-NAC injection reverses markers for inflammation in LPS model of brain injury

Rabbit model of in utero injection of LPS to produce CP from PVL used in Kannan Lab

- Timed pregnant New Zealand white rabbits used and pregnant rabbits in the endotoxin group underwent laparotomies at gestational day 28 (term pregnancy 31 days) and were injected with LPS
- At this dose the newborn kits have been shown to have uniform microglial activation and display a phenotype of CP with predominantly hindlimb hypertonia
- The healthy control group (n=4 dams) included pregnant rabbits that had no surgery or intervention. All kits were born spontaneously on gestational day 31 and were used for the experiments.
Rationale for Dendrimer-NAC therapy for ALD

- Microglial activation, blood-brain-barrier impairment, and neuroinflammation are critical diagnostic markers for ALD in humans.
- Inflammation is a major mechanism of injury.
- NAC (75 mg/kg every 6 hours) is effective as adjunct therapy with bone marrow transplant in patients.
- Dendrimer-NAC overcomes the impaired BBB, is a superior antioxidant, anti-inflammatory agent, targets activated microglia, and produces remarkable improvements in CP.

Relationship between ccALD, and cerebral Palsy

- Pathophysiology in ccALD, and CP is similar with no specific treatment options for each patients, and without conclusive therapy.
- Microglia activation and BBB impairment are hallmark in cc ALD (Kannan et al. Science Translational Medicine, 2012)

Summary of Kennedy Kneger/Johns Hopkins Progress with CPF Support

- Studies of predictive models for early detection of CP in infants from NICU continua.
- Pre-clinical studies of mouse models completed.
- Pre-clinical studies of toxicity in dogs and more completed.
- Strong FDA interest at first meeting, they will schedule a pre-IND meeting for studies in children in ALD who are not narrow transplant candidates.
- Based on results in ALD, FDA will consider IND for children with Cerebral Palsy.

Developmental Brain Injuries

- Asphyxia causing hypoxic-ischemia in term infants and later cerebral palsy, and related disabilities.
- INO: Injured newborn infant; NIH: National Institutes of Health; NICU: Neonatal Intensive Care Unit.
- Children with cerebral palsy and related disabilities have a high prevalence of developmental brain injuries.
- White matter injury from inflammation or ischemia leading to absence of neurons. Parkinson's disease.
- Cell-based therapy with stem cell transplantation improves outcomes.
- Research conducted at the Johns Hopkins Hospital.

How Are We Integrating Basic Knowledge Into Clinical Practice?

- Glutamate mediated excitotoxicity triggers CP through a cascade of injury that can be treated clinically with therapeutic hypothermia and reduction of magnesium influx in neurons with threatened pre-term labor.
- Inflammation is a second major mechanism for CP triggered by hypoxic-ischemia and intrauterine, and pre-chroNic evidence supports CP as a neuroinflammatory disease.
- Neurogenetic and epigenetic mechanisms for disabilities may also trigger these two major mechanisms, leading to therapies for these disorders as well.
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