

NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 7 / Issue 9

September 2012

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Urea Cycle Defect in a Newborn: A Case Report

by Virginia Kaldas, MD; Yuly Carreras, MD; Natasha Acosta, MD; Manuel Castillo, MD; Dora Alvarez, MD; Magda Mendez, MD; Suresh Khanna, MD
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Upcoming Medical Meetings

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Neonatal Nurse Practitioners Symposium: Clinical Update and Review

Oct. 16-20, 2012; Clear Water Beach, FL USA
www.fannp.org/pages/conference.html

Third Port Said Neonatology Conference

Oct. 18-20, 2012; Port Said, Egypt
www.portsaidneogr.com/index.html

Miami Neonatology 2012 - 36th Annual International Conference

Oct. 31-Nov. 3, 2012; Miami Beach, FL USA
pediatrics.med.miami.edu/neonatology/international-neonatal-conference

Contemporary Management of Neonatal Pulmonary Disorders Conference

Nov. 1-2, 2012; Tempe, AZ USA
www.nalweb.com/cmnpdconference

NEONATOLOGY TODAY

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ISSN: 1932-7129 (print); 1932-7137 (online).
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Nehalem, OR 97131 USA

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Manzanita, OR 97130 USA

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Westerly, RI 02891 USA

www.NeonatologyToday.net

Neonatology Today (NT) is a monthly newsletter for Neonatologists and Perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

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Urea Cycle Defect in a Newborn: A Case Report

By Virginia Kaldas, MD; Yuly Carreras, MD; Natasha Acosta, MD; Manuel Castillo, MD; Dora Alvarez, MD; Magda Mendez, MD; Suresh Khanna, MD

Abstract

Surplus nitrogen from the human body is removed by the urea cycle, the major detoxification route in humans. Severe deficiency or total absence of activity of any of the first four enzymes (CPS1, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life. Infants with a severe urea cycle disorder are normal at birth, but rapidly develop cerebral edema and the related signs of: lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma. Clinical presentation is similar to many more common illnesses; an index of suspicion can lead to prompt diagnosis and early institution of proper treatment, and can prevent severe morbidity and mortality. Here we present a report of a 4-day-old infant with urea cycle defect, the diagnostic workup of the infant and management plan. A definitive diagnosis of a Urea Cycle Defect depends on either molecular genetic testing or measurement of enzyme activity. Prenatal genetic testing is available for urea cycle defects.

Case Presentation

A 3,030 gram Hispanic female was born to a 27-year-old woman with normal prenatal labs after an uneventful pregnancy from consanguineous marriage. Perinatal period was reportedly unremarkable except for jaundice from ABO

setup not requiring phototherapy. According to the mother, the infant is being breastfed supplemented with formula. On the fourth day of life, the infant presented to clinic with lethargy, decreased activity and poor feeding. Physical examination revealed an obtunded 2,905 grams infant with icterus, hypothermia, shallow respirations, decreased activity, decreased response to painful stimuli and poor suck. Vital signs T 93.5 F, HR 115 beats/min and respiratory rate 42 breaths/min, oxygen saturating 100% on room air, with a capillary refill > 2 seconds. The remainder of the physical examination was unremarkable.

The infant received intravenous a normal saline bolus, a sepsis workup was performed (spinal tap was deferred) and the patient was then transferred to the Pediatric Intensive Care Unit (PICU) for further management. In the PICU she was started on 10% dextrose solution and empiric antibiotics. Initial laboratory results: Total Bilirubin 15.5 mg/dl, Direct Bilirubin 1.5 mg/dl, WBC 9300, hematocrit 46%, Platelets 330,000, Neutrophils 71%, Lymphocytes: 19%, and Monocytes 8.3%. Serum sodium 147 mmol/L, potassium 5.3 mmol/L, chloride 112 mmol/L, bicarbonate 18 mmol/L, glucose 106 mg/dL, BUN 2 mg/dL, creatinine 0.4 mg/dl, and calcium 8.8 mg/dl. Liver function tests: AST 38 U/L, ALT 19 U/L, Alkaline phosphatase 305 U/L, Total Protein 5.3 g/dl, and Albumin 2.6 g/dl. Venous blood gas testing revealed pH 7.48, PCO₂ 29.6 mmHg, PO₂ 46 mmHg, HCO₃ 22.5 mmol/L, and Lactate 1.4 mmol/L. The chest X-ray, head ultrasound and electrocardiogram were reported as normal. Three hours after admission a phone call from the State Screen Laboratory revealed the underlying diagnosis. The mother was notified about elevated citrulline levels on the State Newborn Screening Test. The Infant Ammonia Level was reported to be 914 Umol/L. The Terti-

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ary Care Center was notified and the infant was transferred for further care (Hemodialysis).

Pathophysiology

Catabolism of amino acids results in the production of free ammonia, which, in high concentration, is extremely toxic to the Central Nervous System. In mammals ammonia is detoxified to urea via the urea cycle. Five enzymes are involved in the synthesis of urea: Carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), argininosuccinate lyase (AL), and arginase. A 6th enzyme, N-acetylglutamate synthetase, is also required for synthesis of N-acetylglutamate, which is an activator (effector) of the CPS enzyme. The incidence of Urea Cycle Defects is 1 in 30,000 live births. These are the most common genetic causes of hyperammonemia in infants. All of the urea cycle disorders are autosomal recessive except for OTC deficiency which is X-linked.

Amino acids	Result	Reference range
Phenylalanine	0.96	<2.50
Methionine	0.63	<1.25
Citrulline	2.13	<0.90
Ornithine	0.49	<2.50
Leucine	1.79	<4.00
Tyrosine	2.41	<7.50
Arginine	0.12	<0.90

Our patient has Citrullinemia (Table 1). There are two types of Citrullinemia; the most common is Type I which is caused by a deficiency of enzyme argininosuccinate synthetase, which leads to accumulation of citrulline in the blood, and is associated with an increase in ammonia levels. The severe form of this disease usually presents in neonatal period. Type II Citrullinemia, which is much less

common, is caused by a deficiency of citrin, a mitochondrial that transports protein, that transports aspartate from mitochondria to cytoplasm. Aspartate is required for converting citrulline to argininosuccinic acid; its deficiency results in increased citrulline and ammonia levels. Usually, a patient with Citrullinemia presents in the neonatal period with intrahepatic cholestasis (Figure 1).

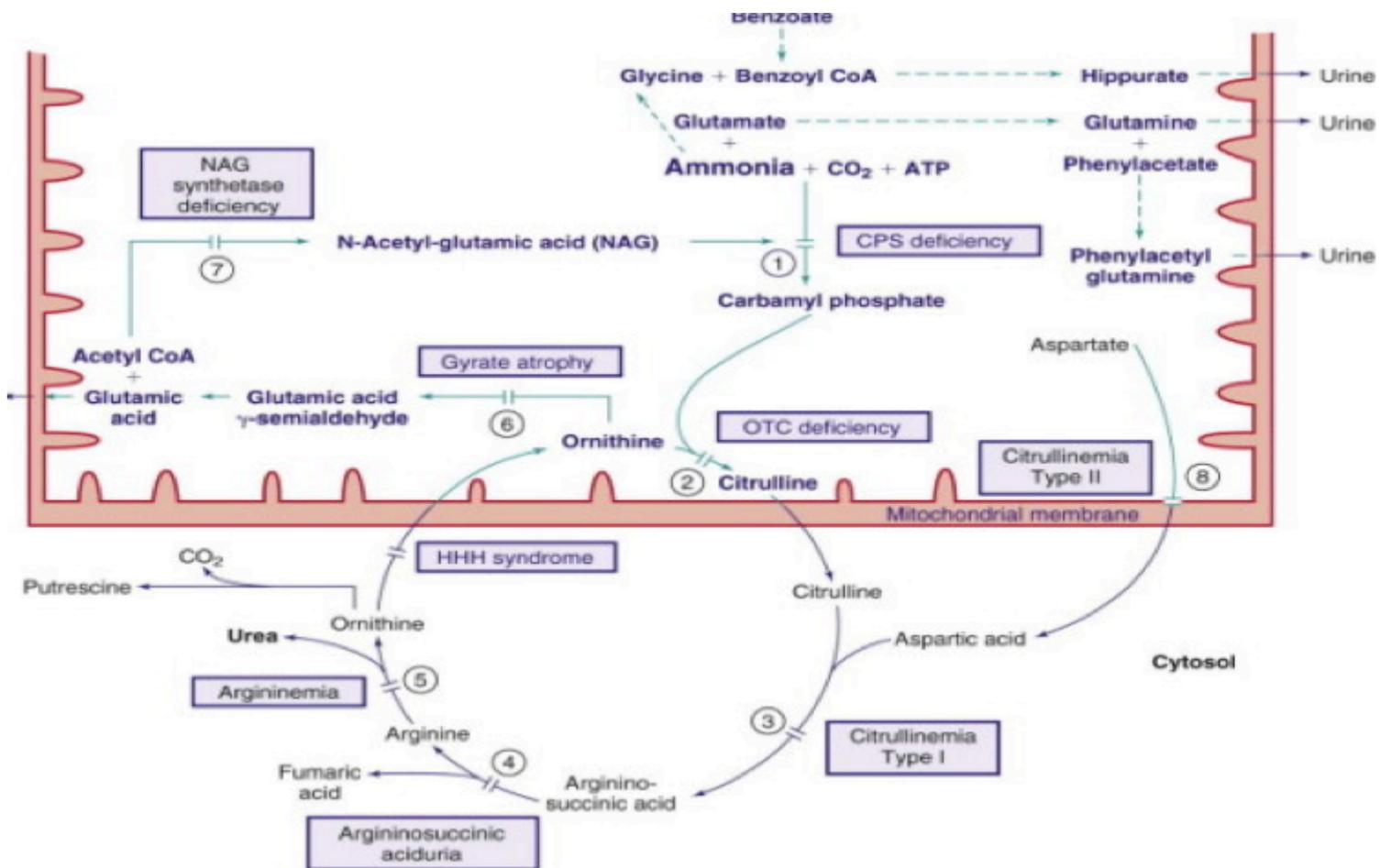


Figure 1. Urea cycle: pathways for ammonia disposal and ornithine metabolism. Reactions occurring in the mitochondria are depicted in purple. Reactions shown with interrupted arrows are the alternate pathways for the disposal of ammonia. Enzymes: (1) carbamyl phosphate synthetase (CPS) (2) ornithine transcarbamylase (OTC). (3) argininosuccinic acid synthetase (AS). (4) argininosuccinic acid lyase (AL). (5) arginase. (6) ornithine-aminotransferase. (7) n-acetylglutamate (NAG) synthetase. (8) citrin HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia. Published with permission: text book of Nelson 19th edition.

Discussion

Infants with Urea Cycle Defect (UCD) are asymptomatic at birth. An infant becomes symptomatic after starting breast or formula feeds (providing protein load). Only 30-40% of infants who present in neonatal period usually have severe enzyme deficiency. Majority of patients present in early childhood or even adulthood. Late presentation is usually due to partial enzyme deficiency. Some patients are diagnosed during the workup for developmental disorder or seizure disorder or some other psychiatric illness.

Infants usually present with: decreased activity, inability to maintain normal temperature, poor feeding, vomiting, lethargy, or even seizure or coma, a presentation typical of infants with sepsis, congenital cardiac disease or other metabolic disorders. A common sign in newborns with hyperammonemia is hyperventilation with respiratory alkalosis. Hyperventilation seems to be due to cerebral edema because of an accumulation of ammonia and other metabolites. Worsening cerebral edema can lead to progressive encephalopathy and central hypoventilation.

In the New York Newborn Screening Program, every infant is screened for 46 inherited metabolic disorders (IMD), and their results are reported to health care providers immediately. Fortunately, in this case, the patient's condition it detected on fourth day of life, our hospital was notified and appropriate treatment was instituted in time.

Infants with bacterial sepsis, other metabolic disorder or congenital heart disease have similar clinical presentation. In case of infection, absence of risk factors or non-diagnostic sepsis workup should prompt physicians to look for other causes. Infants with Congenital Heart Disease (CHD), especially with coarctation of aorta, have similar clinical presentation, but poor distal pulses and differential cyanosis. An echocardiogram is diagnostic in these cases.

Differential Diagnosis

Many infants who have urea cycle defects initially are believed to have sepsis. The difficulty with diagnosing the urea cycle disorders is their lack of biochemical abnormality on routine testing; electrolytes and liver enzyme values usually are normal. An acute presentation is most common

in infants and young children. Trying to distinguish a routine childhood illness from an inherited metabolic disorder can be difficult. Even if there is vomiting, respiratory distress, and eventually encephalopathy (coma), such symptoms most commonly are attributed to infection and sepsis, not to an inherited metabolic disorder. Routine blood tests, cultures, and chest radiographs usually yield unremarkable results.

Transient Hyperammonemia of the Newborn (THAN) is an unusual cause of hyperammonemia and is usually seen in low birth weight infants and low gestational age infants. Clinically these infants have more severe respiratory distress than patients with urea cycle defect. Organic acidemia, fatty acid oxidation defects, etc. should be considered in the differential of infants with hyperammonemia.

Non-genetic causes of hyperammonemia include severe dehydration, hepatic encephalopathy with liver failure, a severe herpes infection can also present with severe hyperammonemia, but this presentation is usually beyond the first week of life.

Diagnostic Workup

An Initial workup should include: complete blood count with differential count; electrolytes, bicarbonate, blood gas, blood urea nitrogen and creatinine. A physician should obtain ammonia levels if the patient presents with: an altered level of consciousness, persistent or recurrent vomiting, primary metabolic acidosis with increased anion gap, or primary respiratory alkalosis in the absence of toxic ingestion. Hyperammonemia and metabolic acidosis with an increased anion gap point to the organic acidemias. Elevation of blood ammonia in conjunction with a normal pH or mild respiratory alkalosis is typical of defects in urea cycle enzymes. When blood ammonia and bicarbonate levels and pH are normal, certain amino acidopathies or galactosemia should be considered.

Therapy

Treatment is urgent in an attempt to avert or mitigate neurologic sequelae and potential death from a treatable cause. Immediate arrangements for hemodialysis should be made and ammonia removal medications (sodium benzoate and sodium phenylacetate) and arginine should

“Although sepsis is your first differential diagnosis when evaluating a severely ill newborn, other conditions should be always considered, including inborn errors of metabolism, and/or Congenital Heart Disease, especially when there are no risk factors for sepsis. An important clue that should stimulate the clinician to look further is the lack of improvement with standard therapy. Failure to diagnose the condition early may lead to irreversible brain injury.”

be administered. Protein intake should be halted if a Urea Cycle Defect or a disorder related to protein “intolerance” such as an organic acidemia is suspected. Such protein deprivation cannot be undertaken without providing appropriate caloric intake from carbohydrates (10% glucose) and an intravenous fat emulsion. If the caloric intake is not sufficient, catabolism of the patient's protein occurs, raising ammonia concentrations in a urea cycle disorder or presenting substrate for the organic acidemias.

Genetic Counseling and Prenatal Diagnosis

All six UCDs can be diagnosed antenatally by chorionic villus biopsies at 9-11 weeks of gestation. All families with UCD should receive genetic counseling. Affected individuals should wear a medical emergency bracelet and carry emergency medical instructions.



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Lesson for the Clinician

Although sepsis is your first differential diagnosis when evaluating a severely ill newborn, other conditions should always be always considered, including inborn errors of metabolism, and/or Congenital Heart Disease, especially when there are no risk factors for sepsis. An important clue that should stimulate the clinician to look further is the lack of improvement with standard therapy. Failure to diagnose the condition early may lead to irreversible brain injury.

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Letters to the Editor

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Medical News, Products & Information

Survival Rates for Premature Babies in High-Level NICUs Are Better Than Previously Reported

Newswise — Philadelphia, July 23, 2012— Premature babies are more likely to survive when they are born in high-level neonatal intensive care units (NICUs) than in hospitals without such facilities, and this benefit is considerably larger than previously reported.

The likelihood that an extremely premature baby will survive if born in a high-technology, high-volume hospital unit was already known, but the current study, the largest to date, revealed a stronger effect. Pediatric researchers who analyzed more than 1.3 million premature births over a 10-year span found that the survival benefits applied not only to extremely preterm babies, but also to moderately preterm newborns.

The research team performed a retrospective study of all hospital-based deliveries of infants with a gestational age between 23 and 37 weeks in Pennsylvania, California and Missouri—a total of over 1,328,000 births. The study focused on preterm deliveries in high-level NICUs, compared to preterm deliveries at all other hospitals.

“Prior studies from the early 1990s found increased survival rates of 30 to 50% among preterm infants delivered at high-level NICUs, compared to preterm infants delivered elsewhere,” said study leader Scott A. Lorch, MD, a neonatologist at The Children’s Hospital of Philadelphia. “However, our research found rates as high as 300% improvement, when our study design controlled for the effect of sicker patients who typically deliver at high-level NICUs.” Complication rates were similar for both types of hospitals.

The retrospective study, which appeared online July 9th in the journal *Pediatrics*, analyzed records for all births occurring between 1995 and 2005 in Pennsylvania and California, and all births between 1995 and 2003 in Missouri. Lorch added that the results varied slightly among the states, possibly reflecting state-level differences in health policies, such as whether or not the state government designated hospitals within a regional perinatal system.

Premature babies are those born before 37 weeks gestational age (full-term is 40 weeks). In this study, the researchers defined extremely preterm infants as those born before 32 weeks and moderately preterm infants as those born between 32 and 37 weeks. They defined a high-level NICU as a Level III facility that delivered at least 50 very low birth weight infants annually. “We found survival benefits in high-level NICUs for both extremely premature and moderately premature infants,” said Lorch. “This suggests that the choice of a delivery hospital may influence the outcomes for the full range of preterm infants.”

Unlike many previous analyses of birth outcomes, said Lorch, the current study covered more than a single state system. Using hospital data from states in three regions of the country suggests that the results may be more generalizable throughout the United States than in more limited studies, he added.

“However,” concluded Lorch, “this research does not imply that every hospital should aspire to build a high-tech NICU—there just aren’t enough babies born prematurely for every birth hospital in the US to have a high-level, high-volume NICU. Instead, the results may assist health care policymakers in organizing regional and statewide care systems to more efficiently provide the best care for premature infants within a geographical area.”

Financial support for this study came from the Agency for Healthcare Research and Quality, part of the US Department of Health and Human Services. Lorch’s co-authors were Michael Baiocchi, PhD and Dylan S. Small, PhD, of the University of Pennsylvania, and Corinne E. Ahlberg, MS, of The Children’s Hospital of Philadelphia. In addition to his position as an attending neonatologist at Children’s Hospital, Lorch is also on the staff of the Hospital’s Center for Outcomes Research and is a senior fellow at the Leonard Davis Institute of Health Economics at the University of Pennsylvania.

“The Differential Impact of Delivery Hospital on the Outcomes of Premature Infants,” *Pediatrics*, published online July 9, 2012, and in print, August 2012. doi: 10.1542/peds.2011-2820

For more information, visit www.chop.edu.

Research and Philanthropy Leaders Focus Agenda on Preterm Birth— 2nd Leading Cause of Death for Children

Leaders of prominent, international philanthropic and research organizations convened in Seattle July 14th-16th to address the global crisis of preterm birth and develop an action roadmap of research priorities and opportunities.

Led by the Bill & Melinda Gates Foundation, the Global Alliance to Prevent Prematurity and Stillbirth (an initiative of Seattle Children’s), the March of Dimes Foundation, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, attendees identified specific, strategic areas of research critical for understanding the causes and mechanisms of preterm birth. This knowledge will provide the basis for identifying barriers and developing strategies and solutions to prevent preterm birth.

The summit comes just two months after the release of *Born Too Soon: The Global Action Report on Preterm Birth*, showing that the number of preterm births around the world has increased to 15 million per year, with more than one million of those babies dying in infancy. As a result, prematurity is now the second-leading cause of death in all children under age five.

In 2009, the *International Conference on Prematurity and Stillbirth* yielded the *Global Action Agenda*, a comprehensive set of recommendations that include milestones and success metrics for preventing prematurity and stillbirth and improving related maternal, newborn and child health outcomes.

The meeting, *Accelerating Research and Development to Address the Global Crisis of Preterm Birth*, will build on the groundwork laid by the Global Action Agenda and the Born Too Soon report, while also exploring the magnitude of the lifelong health problems resulting from preterm birth and determining what is needed for research and development to reduce preterm birth worldwide.

It is a critical time to invest in research in countries with the highest burden and fewest solutions, to advance understanding of the multiple



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and complex causes of preterm birth, and to test new strategies to prevent preterm birth that are low-cost, practical, and feasible.

•“The Bill & Melinda Gates Foundation is committed to improving maternal, newborn and child health, and we know that working in partnership to address preterm birth is essential for mothers and their infants around the world to survive and remain healthy.”

Study Shows Physiological Markers for Neonate Pain

Newswise — There was a time when a belief was widely held that premature neonates did not perceive pain. That, of course, has been refuted but measurements of neonate pain tend to rely on inexact measures, such as alertness and ability to react expressively to pain sensations. Researchers at Loma Linda University reported in *The Journal of Pain* that there is a significant relationship between procedural pain and detectable oxidative stress in neonates.

Previous studies have shown an approach involving measurement of systemic biochemical reactions to pain offers the benefit of providing an objective method for measuring pain in premature neonates. Exposure to painful procedures often results in reductions in oxygen saturations and tachycardia, but few studies have quantified the effects of increased pain oxygen consumption. No studies have examined the relationship between pain scores that reflect behavioral and physiological markers of pain and plasma markers of ATP utilization and oxidative stress.

In this study, 80 preterm neonates were evaluated. In about half, tape was taken off the skin following removal of catheters, and they were evaluated for oxidative stress by measuring uric acid and malondialdehyde (MDA) concentration in plasma before and after the procedure. These subjects were compared with a control group not experiencing tape removal. Pain scores were assessed using the Premature Infant Pain Profile. The data showed there was a significant relationship between procedural pain and MDA, which is a well accepted marker of oxidative stress.

There were increases in MDA in preterm neonates exposed to the single painful procedure and not in the control group. Since premature neonates undergo several painful procedures a day, the researchers concluded that if exposure to multiple painful procedures is shown to contribute to oxidative stress, biochemical markers might be useful in evaluating mechanism-based interventions that could decrease adverse effects of painful procedures.

For more information on American Pain Society, visit www.ampainsoc.org.

Blood Test for Pregnant Women Could Predict Risk of Having Dangerously Small Babies

Researchers from the Ottawa Hospital Research Institute (OHRI) and the University of Ottawa (uOttawa) have found a protein in the blood of pregnant women that can predict if they are likely to have a fetus that doesn't grow properly, and thus has a high risk of stillbirth and long-term health complications. The research, led by Dr. Andrée Gruslin, could lead to a widely available blood test and could help develop ways for improving the outcomes of women and their children who face this risk — estimated to be as many as one of every 20 pregnancies.

Dr. Gruslin's study, published in the *Journal of Clinical Endocrinology and Metabolism*, focuses on a protein called Insulin Growth Factor Binding Protein 4 (IGFBP-4). While this protein has been linked to pregnancy before, this study is the first to demonstrate its important role in human pregnancy complications. A key part of the study involved examining IGFBP-4 levels in first trimester blood samples from women who partici-

FEBRUARY MEDICAL MEETING FOCUS

NEO Conference and NEO CQI Pre-Conference

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Selected Agenda Topics from NEO CQI (Feb. 20th)

Moderated by Drs. Dan Ellsbury and Robert Ursprung

- Quality Improvement and Maintenance of Certification in Pediatrics
- How to Improve: Basic Techniques
- Reducing Catheter Associated Infections
- Reducing Necrotizing Enterocolitis
- Reducing Retinopathy of Prematurity
- Improving Admission Thermal Management
- Decreasing Bronchopulmonary Dysplasia
- Optimizing NICU Medication Use
- Improving Antibiotic Stewardship
- Creating a Culture of Quality and Safety

Selected Agenda Topics from NEO (Feb. 21st-24th)

- Conventional Versus High Frequency Ventilation - *R. Clark, MD*
- Non-Invasive Respiratory Management of the Neonate - *E. Bancalari, MD*
- The Pharmacology of Chronic Pulmonary Hypertension - *S. Abman, MD*
- Hazards and Uses of Post-Natal Steroids - *David Burchfield, MD*
- The Genomics of Perinatal Care - *Joann Bodurtha, MD*
- Non-Invasive Fetal Testing - *Richard Porreco, MD*
- Perinatal Evaluation and Management of Growth Restriction - *T. Garite, MD*
- The Management of Neonatal Pain - *R. W. Hall, MD*
- Limiting Antibiotic Exposure in the NICU - *D. Benjamin, MD*
- Neonatal Abstinence Syndrome (NAS) and the NICU - *E. Gauda, MD*
- The Baby at Borderline Viability—Is Anything Changing - *W. Meadow, MD*
- Assisting Parents with Difficult Decisions in the NICU: Ethical Considerations - *M. Mercurio, MD*
- When is the Standard of Care Standard? - *J. Fanaroff, MD*
- Legends of Neonatology Gala - 2013 Honorees: *Lilly Dubowitz, MD; Jen-Tien Wung, MD; Jeffrey Maisels, MB, B.Ch., DSc.*
- The Impact of Growth on Neonatal Outcome - *R. Ehrenkrantz, MD*
- Nutrition and the Neonate—Are We Sure What We Are Feeding Babies? - *A. Spitzer, MD*
- Breast Milk Use in the NICU—Is It Safe, Is It Adequate? - *P. Meier, DNSc, RN*
- The Refluxing Preemie—Is This a Problem? - *R. Martin, MD*
- Decreasing CVL Infection - *M. McCaffrey, MD*
- Reducing Bronchopulmonary Dysplasia—Is This Possible? - *N. Ambalavanan, MD*
- Necrotizing Enterocolitis - *M. Blakely, MD*
- Retinopathy of Prematurity - *D. Phelps, MD*

See website for additional detail

pated in a large study of pregnancies and newborns called the Ottawa and Kingston (OaK) birth cohort.

Dr. Gruslin found that women with high levels of IGFBP-4 were 22 times more likely to give birth to tiny babies (defined as the smallest five per cent by weight for their gestational age), than women with normal levels of IGFBP-4. This part of the study involved a total of 72 women — half with tiny babies and half with normal weight babies.

"Usually, we don't find out until later in a pregnancy that a fetus isn't growing properly, but this test can tell us in the first trimester if there's

likely to be a problem," said Dr. Gruslin, a Scientist at OHRI, High Risk Obstetrician at The Ottawa Hospital and Professor on the Faculty of Medicine at uOttawa. "By identifying these high-risk pregnancies early on, we will be able to monitor these women more closely and hopefully help them deliver a healthier baby."

The IGFBP-4 blood test is still experimental, but Dr. Gruslin hopes to develop a refined version that could be made available to all pregnant women within the next couple of years. She also hopes that her studies on IGFBP-4 could lead to new approaches that would improve fetal growth in high-risk pregnancies. This condition, called Fetal Growth Restriction or Intrauterine Growth Restriction, is thought to affect three to five per cent of all pregnancies, and cause close to half of all stillbirths. Babies born with this condition also have a higher risk of developing serious health complications in infancy and childhood, as well as chronic diseases such as hypertension and diabetes in adulthood.

Fetal Growth Restriction is thought to occur when the placenta, which provides nourishment and oxygen for the fetus, doesn't grow properly. Research by Dr. Gruslin and others suggests that IGFBP-4 blocks the activity of a key placental growth hormone called IGF-II, which results in poor growth of the placenta and fetus. Dr. Gruslin and her team are already testing a number of strategies for targeting IGFBP-4 to improve placental and fetal growth.

This study was funded by the Canadian Institutes of Health Research and the National Key Basic Research Program of China, and was conducted by researchers at OHRI, uOttawa, the Chinese Academy of Science and Third Hospital of Hebei Medical University in China. The paper is titled "Significance of IGFBP-4 in the development of fetal growth restriction" by Qing Qiu, Mike Bell, Hongmei Wang, Xiaoyin Ly, Xiaojuan Yan, Marc Rodger, Mark Walker, Shi-Wu Wen, Shannon Bainbridge and Andrée Gruslin.

Research at Ottawa Hospital Research Institute (OHRI) is supported by The Ottawa Hospital Foundation. www.ohri.ca.

Study Examines Risk Factors for Visual Impairment Among Preschool Children Born Extremely Preterm

Cerebral damage and retinopathy of prematurity appear to be independently associated with

visual impairment among preschool children who were born extremely premature, according to a report published Online First by *Archives of Ophthalmology*, a JAMA Network publication.

Retinopathy of prematurity (ROP), an eye disease in very premature infants, is considered the main cause of visual impairment in extremely preterm children, however cerebral damage is also a cause of visual impairment (often referred to as cerebral visual impairment) among extremely preterm children, according to background information in the study.

To examine the importance of cerebral damage and retinopathy of prematurity for visual impairment in preschool children who were born extremely premature, Carina Slidsborg, MD, from Copenhagen University Hospital, Glostrup Hospital and Rigshospitalet, Denmark, and colleagues conducted a clinical follow-up study of a Danish national cohort of children.

The authors included 178 extremely premature children (gestational age <28 weeks) born between February 13, 2004 and March 23, 2006, and a matched control group of 56 term-born children (gestational age 37 to <42 weeks) in the analysis.

Analysis found that global developmental deficits (an indicator for cerebral damage) and foveal sequelae (abnormalities involving the fovea, a small area of the retina responsible for sharp vision) occurred more often in extremely preterm children than in term-born children, and increased with ROP severity. The authors also found that global developmental deficits, moderate to severe foveal abnormality, and ROP treatment were independently associated with visual impairment.

"In conclusion, we herein demonstrate that, in Denmark, cerebral damage and ROP sequelae are independent risk factors for VA loss among preschool children born extremely premature and that the presence of cerebral damage is the primary risk factor of the two," the authors conclude.

(Arch Ophthalmol. Published online June 11, 2012. doi: 10.1001/archophthalmol.2012.1393.

This work was supported by grants from the Danish Eye Health Society, Bagenkop Nielsens Myopia and Eye Foundation, VELUX Foundation, Aase and Ejnar Danielsen Foundation, Dagmar Marshall Foundation, Direktør Jacob Madsen and Hustru Olga Madsen

Foundation, PA Messerschmidt, and the Hustrus Foundation.

The National Institute of Standards and Technology (NIST) Has Released a Guide to Help Improve the Design of Electronic Health Records for Pediatric Patients

While hospitals and medical practices are accelerating their adoption of electronic health records, these records systems often are not ideal for supporting children's health care needs. Young patients' physiology is different from adults—and varies widely over the course of their growing years. Tasks that are routine in larger bodies can be complex in smaller ones, and pediatric patients typically cannot communicate as fully as adults.

These and other challenges can create additional physical and mental demands on the professionals who treat children, and affect the way they interact with an electronic health record. This makes the selection and arrangement of information displays, definition of "normal" ranges and thresholds for alerts in pediatric electronic health records more challenging to design and implement than those created for adults.

The new NIST guide was developed with the help of experts in pediatrics, human factor engineering, usability and informatics (which brings together information science, computer science and health care). The guide was peer-reviewed by both human factors experts and clinicians as well as other professionals in leading pediatric health care organizations in the United States and Canada.

The document offers technical guidance to help the designers of pediatric electronic health records create systems that can be used as intended, efficiently and effectively. Its recommendations include adopting a user-centered design approach that is informed by scientific knowledge of how people think, act, and coordinate to accomplish their goals. It also focuses on critical user interactions—those that can potentially lead to errors, workarounds, or adverse events that can harm patients.

A Human Factors Guide to Enhance EHR Usability of Critical User Interactions when Supporting Pediatric Patient Care (NISTIR 7865) is available



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Medical Complications in Hospitalized Children: The Canadian Paediatric Adverse Events Study

More children experience complications or unintended injuries, especially related to surgery, in academic hospitals compared with community hospitals, but adverse events in the former are less likely to be preventable, according to the Canadian Paediatric Adverse Events Study published in *CMAJ (Canadian Medical Association Journal)*.

Children are especially vulnerable to harms associated with medical care, such as medication errors, surgical complications and diagnostic errors.

A team of Canadian researchers undertook the Canadian Paediatric Adverse Events Study to determine the frequency, type, severity and preventability of harmful events in children in academic pediatric centres compared with those in community hospitals in Canada. They looked at medical charts of 3,669 children admitted to hospital from April 2008 to March 2009 at 8 academic pediatric centres and 14 community hospitals in 7 provinces.

They found that 11.2% of children in academic centres had adverse events compared with 3.3% in community hospitals. The events occurring in academic hospitals were more likely to be non-preventable than those in community hospitals. Adverse events were highest in surgical patients (35.1%), followed by medical patients (29.8%) and ICU patients (13.3%). Emergency and maternal/obstetric adverse events were more common in community hospitals while surgical and ICU events were more frequent in academic centres.

The higher rate of adverse events for children in teaching hospitals has been previously reported. The authors suggest it may be because there are more patients in these centres with complex illnesses, more caregivers and more handoffs between caregivers, health care trainees and other factors.

"We found a predominance of adverse events related to surgery," writes Dr. Anne Matlow, former Medical Director, Patient Safety, The Hospital for Sick Children (SickKids), currently Vice-President, Education, Women's College Hospital, with co-authors. "This high incidence in academic centres could be explained by the Canadian practice of performing most surgery in children under 5 years of age in such facilities."

"Our findings are likely not unique to Canada. Risk factors for unsafe care in pediatrics are universal, including children's physical characteristics and developmental variability," conclude the authors. "We hope our results will catalyze widespread efforts to improve pediatric health care in Canada."

The study was conducted by researchers from the University of Toronto, University of British Columbia; University of Calgary; University of Alberta; University of Manitoba; Université de Montréal; Dalhousie University and Memorial University. The two major funders were SickKids and the Canadian Patient Safety Institute.

New Study Finds External Stimulation Impacts White Matter Development in the Postnatal Brain

A team at Children's National Medical Center in Washington, DC has found that external stimulation has an impact on the postnatal development of a specific region of the brain. Published in *Nature Neuroscience*, the study used sensory deprivation to look at the growth and collection of NG2-expressing oligodendrocyte progenitor cells (NG2 cells) in the sensory cortex of the brain. This type of research is part of the Center for Neuroscience Research focus on understanding the development and treatment of white matter diseases.

NG2 cells can develop into oligodendrocytes progenitor cells that generate myelin, the protective material around the axons of neurons, but this is based on functional and developmental interactions with outside stimuli. With this kind of plasticity, or ability to change and mold a cell in different ways, the researchers were able to determine that sensory stimuli can control the number and positioning of developing NG2 cells.

"Understanding how external stimulation and experience impact the development of NG2 cells means that we can try to modulate these factors to help regulate and promote the expansion of these cells. This could ultimately have an impact on white matter diseases," stated Vittorio Gallo, PhD, study coordinator and Director of the Center for Neuroscience Research at the Children's Research Institute. "We will now investigate in more detail how sensory experience can regulate NG2 cell development, particularly how experience activates specific genes and molecular pathways in these cells."

Collectively called NG2 progenitors, these cells also serve as the primary source of cells to regenerate oligodendrocytes and myelin in the postnatal brain. Without myelin, the brain does not function properly. Myelination can be impaired for a number of reasons, resulting in mental retardation and developmental disabilities. Myelination, white matter growth and repair, and the study of complex mechanisms of pre- and postnatal brain development are a key focus of the Center for Neuroscience Research at Children's National, which also houses the White Matter Diseases Program, one of the largest clinical programs in the country for treating children with disorders that cause the brain's white matter to degenerate.

Read the study abstract in *Nature Neuroscience* - www.nature.com/neuro/journal/vaop/ncurrent/full/nn.3190.html.

Learn more about Children's National Center for Neuroscience Research of the clinical care that Children's provides through the White Matter Disease Program at: www.childrensnational.org

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Neonatology Clinical Trials

Exploratory Propofol Dose Finding Study in Neonates (NEOPROP)

Official Title: Prospective Exploratory Dose-finding Study in Neonates Receiving a Single Intravenous Propofol Bolus for Endotracheal Intubation During (Semi-) Elective INSURE Procedure or Non-INSURE Procedures in Neonates

This study is currently recruiting participants.

Sponsor: Universitaire Ziekenhuizen Leuven

Information provided and verified by: Universitaire Ziekenhuizen Leuven

ClinicalTrials.gov Identifier: NCT01621373

Study Type: Interventional

Study Design: Endpoint Classification: Pharmacokinetics/Dynamic Study

Intervention Model: Single Group Assignment

Primary Purpose: Treatment

Further study details as provided by Universitaire Ziekenhuizen Leuven:

Primary Outcome Measures: Number of neonates where successful in- and extubation in INSURE conditions and successful intubation in non-INSURE conditions is achieved [Time Frame: 1 hour after propofol administration] [Designated as safety issue: No]. Using predefined scoring systems we will evaluate in how many patients successful intubation and extubation in INSURE-conditions was achieved. In non-INSURE conditions only successful intubation will be evaluated. Afterward we will explore the given dose of propofol in each stratum to reach this outcome measure.

Estimated Enrollment: 50

All patients receive propofol. Dose will be defined based on response of previous patient in the same stratum.

Drug: propofol administration; Single IV bolus propofol start at 1 mg/kg. Dose will be adapted based on predefined scoring systems with +/-0.5 mg/kg.

Detailed Description: The aim of the study is to evaluate the pharmacokinetics and pharmacodynamics of propofol (short acting anesthetic) in 50 neonates to whom the drug is administered as an intravenous bolus. This is part of routine clinical care in patients receiving

(semi-) elective intubation. It's the aim to explore the most effective IV propofol dose for a successful INSURE (intubation, surfactant, extubation) procedure and for successful (semi-) elective intubation in non-INSURE procedures. We hereby aim to define the most optimal dose regimen for propofol in neonates, and will use:

- predefined scoring systems to evaluate sedation, relaxation and intubation conditions
- vital parameter monitoring
- pharmacokinetic analysis with blood samples
- brain monitoring with NIRS derived cerebral oxygenation and aEEG.

Ages Eligible for Study: Up to 28 Days

Genders Eligible for Study: Both

Accepts Healthy Volunteers: No

Inclusion Criteria: Neonates admitted to the Neonatal Intensive Care Unit (NICU) who need short procedural sedation for (semi-) elective intubation will be considered for inclusion, after informed written consent of the parents. Patients can be included if they are hemodynamically stable and did not receive sedative or analgesic agents during the previous 24 hours.

Exclusion Criteria: Known propofol intolerance

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Locations: Neonatal Intensive Care Unit UZ Leuven, Belgium

Responsible Party: Universitaire Ziekenhuizen Leuven

Health Authority: Belgium: Federal Agency for Medicinal Products and Health Products

ClinicalTrials.gov Identifier:
NCT01621373

Other Study ID Numbers: s54472, 2012-002648-26

Study Start Date: August 2012

Estimated Study Completion Date:
August 2013

For up-to-date information on this trial and others, please visit: www.ClinicalTrials.gov

NEONATOLOGY TODAY

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ISSN: 1932-7129 (print); 1932-7137 (online).
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