Early warning of newborn withdrawal

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In substance-exposed newborns, identification of the gene variations associated with risk of opioid addiction could aid the treatment of their withdrawal symptoms in the critical hours after birth, according to a University of Maine psychology researcher.

A new study has found that single-nucleotide polymorphisms (SNPs) predict withdrawal symptoms severity in infants prenatally exposed to methadone, an opiate used to treat maternal dependence. Hospital stays were shorter for those newborns who had gene variants or polymorphisms in their OPRM1, related to opiate addiction in adults, and COMT, associated with brain neurotransmitter dopamine and frontal cortex, according to the study by UMaine Professor of Psychology Marie Hayes and recent UMaine doctoral student Jonathan Paul, in collaboration with Dr. Mark Brown at Eastern Maine Medical Center in Bangor and colleagues at Tufts Medical Center.

The findings of the study of 86 opiate dependent mothers and their newborns were published on May 1 in the *Journal of the American Medical Association* (*JAMA*). The study is considered the first to examine the association of genetics and opioid withdrawal in newborns in an effort to better understand neonatal abstinence syndrome (NAS).

"OPRM1 is most important in determining if an infant has an easier or harder withdrawal process based on having the addiction risk genetic profile," says Hayes, who also has a joint appointment in the UMaine Graduate School of Biomedical Sciences and Engineering. "Adults with OPRM1 and COMT risk alleles have increased need for opioids to control the pain of chronic disease, such as cancer. If babies have one or both, they may require more opioid to control their withdrawal.

"The clinical significance is that when we genetically test the mothers (for these genes) or the babies in the postnatal period, we may be able to predict if the opioid-exposed babies will have easy or difficult withdrawal and plan replacement medications accordingly," says Hayes, who is an allied scientist in pediatrics, family medicine and psychiatry at Eastern Maine Medical Center in Bangor.

At issue are the severe, potentially life-threatening withdrawal symptoms in newborns that can lead to complications, such as seizures and regulatory instability in feeding and sleep. Understanding which newborns are genetically more at risk and in need of aggressive treatment could temper potential long-term outcomes of severe withdrawal on child brain development.

Knowing the mother's variation in OPRM1 and COMT genes, coupled with a blood test of the newborn, could provide early warning that the baby is at risk for severe withdrawal symptoms and allow parents and caregivers to plan accordingly.

Seventy percent of babies born to mothers with opiate addiction, including those in methadone programs, experience the same abstinence symptoms as adults. Withdrawal symptoms can begin in the first 48 to 72 hours after birth and last for weeks or months, interfering with neuronal and respiratory development, says Hayes, who has been studying the effects of substance exposure on newborns for the past seven years.

Since 2009, that research has included the collection of genetic data as part of a longitudinal study of mothers and their substance-exposed newborns, led by Hayes and Dr. Mark Brown, chief of pediatrics and director of nurseries at Eastern Maine Medical Center.

In 2011, Hayes and Brown began collaborating with Drs. Jonathan Davis and Elisha Wachman at Tufts Medical Center to determine which genes would be most helpful in predicting severity of withdrawal symptoms and, ultimately, most effective treatments and lengths of hospital stays.

Their research is part of a $3 million, multi-institution National Institutes of Health (NIH) study led by Davis at Tufts Medical Center and Barry Lester at Brown Medical School. Hayes is a member of the steering committee on the associated clinical trial, providing expertise on genetic polymorphisms and developmental outcomes in NAS infants.

The first findings of the collaborative research with Wachman and Davis at Tufts Medical Center, and Hayes were reported in *JAMA*. The research team also included Jonathan Paul, a former UMaine doctoral researcher under Hayes who helped develop the genetic model and who is now an NIH postdoc at the University of Texas Medical Branch.

This is the second time in the past year that Hayes' NAS research has been highlighted in the prestigious medical journal. A year ago, *JAMA* featured an editorial by Hayes and Brown, "The Epidemic of

Prescription Opiate Abuse and Neonatal Abstinence," detailing the challenges of caring for this vulnerable population, cautioning against defunding maternal treatment programs, and calling for stepped-up research into effective medications and other protocols.

More research is needed to better understand just what NAS treatment should be—and the results without it.

"I feel strongly that babies should be treated early and aggressively (with opioids) so that excessive excitation of the brain associated with withdrawal is mitigated, precluding seizure risks and damage to the brain. Treating aggressively prevents potential neurotoxicity incurred when experiencing withdrawal symptoms, with opioids being, perhaps, the lesser of two evils," says Hayes, who organized a May 3 symposium on NAS, chaired by JAMA editor Howard Bauchner, in conjunction with the Pediatric Academic Societies conference in Washington, D.C.

"Doctors feel that the type of postnatal opiate treatment is critical and that more opiate exposure should be avoided in the postnatal period if possible. That's one of the critical questions in the research at this time," she says.

As a result of the now 4-year-old longitudinal study at UMaine, Hayes and her team—recent Ph.D. Beth Logan and grad students Nicole Heller, Deb Morrison and Hira Shrestha—have collected information of more than 200 NAS infants, tracking their development up to 3 years of age. Upcoming research papers will focus on methadone-related prenatal exposure and its effects on an NAS infant's brain development, and what EEG results reveal about the neurocognitive effects of NAS in the first three months of life.

In addition, Hayes' lab also is working with neurogeneticist David Nielson at Baylor College of Medicine to test other polymorphisms and

their effects on NAS. In particular, they are looking at the methylation of opiate and related stress and addiction genes that would result in longer-term changes in gene expression over time, based on babies' prenatal exposure and severity of withdrawal course.

Provided by University of Maine

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