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Impact of Early Childhood Adversity Depends on Genes

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June 23, 2011 (New Orleans, Louisiana) — Early adversity exerts negative influences that can be observed at the cellular level, highlighting the need for early intervention for at-risk children in adverse environments, new research suggests.

"Genetic plasticity may explain significant amounts of variation in both susceptibility to and recovery from early adversity. Early adversity not only results in lasting vulnerability for a range of adverse outcomes but also may lead to detectable epigenetic changes," said principal investigator, Stacy Drury, MD, PhD, of Tulane University Medical School, New Orleans, Louisiana.

Dr. Drury presented findings from the Bucharest Early Intervention Project (BEIP) here at the 16th Annual International "Stress and Behavior" Neuroscience and Biopsychiatry Conference.

BEIP is the only randomized controlled trial of foster care compared with continued institutional care. The aim was to look for differences in behavior in middle childhood between the 2 cohorts and examine associations between genotype and outcomes.

"Across studies, early adversity is a risk factor for a range of negative outcomes. Recent theories have begun to challenge the vulnerability/resilience concept of gene-environment interactions, suggesting instead that these interactions are better characterized in terms of biological sensitivity to context. In this model, genetic variation results in greater sensitivity to the environment, for better or worse. Further, the influence of epigenetic changes may be additional potential contributors," said Dr. Drury.

Extreme Early Adversity

Early care in institutions such as orphanages is an extreme form of early adversity and a known risk factor for psychological, cognitive, and physical negative outcomes.

The BEIP was an examination of "genetic plasticity" and the occurrence of reactive attachment disorder, which is primarily a result of extreme adverse caregiving. These children fail to exhibit appropriate, selective social attachment when they are developmentally capable, she explained.

The investigators also examined the association between cumulative exposure to institutional care and telomere length, an epigenetic marker previously linked to psychosocial stress and early adversity.

The study included 136 Romanian children, aged 6 to 30 months, currently residing in 1 of 6 different institutions in Bucharest, Romania. The children received a comprehensive baseline assessment and then were randomized to either continued institutional care, known as the care-as-usual group (CAUG), or to foster care placement (FCG) at

younger than 31 months and followed up longitudinally. Careful life histories on each child were maintained until 54 months of age.

The government-sponsored foster care system was established in Romania as an intentional alternative to institutional care.

Indiscriminate behavior was assessed at 4 time points by caregiver report using the Disturbances of Attachment Interview (DAI). Investigators examined the association of indiscriminate behavior at each time point with functional polymorphisms in 2 genes previously associated with differential susceptibility to early adversity: brain-derived neurotrophic factor (BDNF) val 66met and the serotonin transporter (5HTT) 5httlpr.

Because these 2 polymorphisms have been found to have an additive influence on outcomes, they explored the association between indiscriminate symptoms and a combined plasticity genotype (met allele carriers and s/s/homozygotes).

Finally, they examined the association between cumulative exposure to institutional care and telomere length, using quantitative polymerase chain reaction to determine the telomere repeat unit to single copy (T/S) ratio when the children were between 6 and 10 years of age. They also looked for associations between telomere length and cumulative percentage of time in institutional care before 54 months of age.

Genotype Modified Response

Investigators found that scores on the DAI were related to genotype and that institutionalization was associated with shorter length of telomeres in middle children, Dr. Drury reported.

"To our knowledge this is the first study to demonstrate genetic biological sensitivity to context in the same children exposed to well-defined changes in the caregiving environment associated with institutional rearing," she said.

It is also the first study to find an association between adversity and telomere length in children and contributes to the growing literature linking telomere length and early adversity.

The study also showed that DAI scores changed significantly only in children with a "responsive" genotype, she said.

Children with the s/s 5httlpr genotype or carriers of the met 66 allele in BDNF demonstrated both the greatest decrease in DAI scores in the FCG (indicating improvement) and the highest persistent rate of indiscriminate social behavior in the CAUG, Dr. Drury reported.

Regression analysis showed that 5httlpr genotype had the greatest impact on change in DAI score between baseline and 42 months (P = .02), whereas the most impact of BDNF genotype occurred between 30 and 54 months (P = .003).

Children with both s/s 5httlpr genotype and met/allele carriers of BDNF in the CAUG had the highest number of indiscriminate symptoms at 54 months, whereas those with the same genotype in the FCG had the lowest number.

In other words, whether children remained institutionalized or were sent to foster care had less impact on outcome than whether they harbored a "plasticity" genotype, which apparently modified their response to the caregiving. A plasticity genotype is "not necessarily all bad" but in combination with adversity is associated with worse outcomes, she explained.

Shortened Telomeres, Longer Institutionalization

The mechanism of how these early adverse experiences alter biological processes is not fully understood, but one explanation may lie within the telomeres.

Accelerated telomere shortening, or cellular aging, has been associated with psychological stress and early adversity in adults and is linked to various diseases in adulthood, but the BPEI may be the first to examine this association in children.

The BPEI examined the association between average relative telomere length, T/S ratio, and exposure to institutional care quantified as the percentage of time at baseline and at 54 months of age that each child lived in the institution.

A significant negative correlation was observed between T/S ratio and percentage of institutionalized time. Children with greater exposure to institutional care had significantly shorter relative telomere length in middle childhood. This was true both for time spent at baseline (P = .0128) and at 54 months (P = .0420).

Telomere length may represent an objective epigenetic biomarker of early adversity and putatively 1 mechanism by which early adversity “gets under the skin and into our biology,” she said.

Duration of Adversity Predicts Telomere Length

The results remained significant after adjusting for group assignment (FCG vs CAUG), sex, ethnicity, low birth weight, and age at telomere collection. The greatest proportion of variance in length was explained by the percentage of time spent in institutionalized care at baseline.

Sex modified this main effect, she added. The percentage of time in institutional care at baseline significantly predicted telomere length in females, whereas the percentage of institutional care at 54 months was strongly predictive of telomere length in males.

"Cumulative early exposure to an adverse environment predicted telomere length in individual children. We are going to look at the telomeres annually to look for a ‘critical window’ during which telomere shortening might be prevented," Dr. Drury said.

Jeffrey Tasker, PhD, director of the Neuroscience Program at Tulane University School of Medicine, said the study adds a "very interesting human perspective on stress plasticity.

"It relates the human cognitive aspects of early life stress to some of the genetic and cellular mechanisms that people are looking at. The exact relationship between telomere length and phenotypes is still not clear, but the study found some promising correlations."

Dr. Drury and Dr. Tasker have disclosed no relevant financial relationships.

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