Infants Found to Have Alzheimer’s Risk Gene Show Brain Differences

BY JAMIE TALAN

With growing evidence that young adults who carry one or two copies of the apolipoprotein E4 (APOE) gene have reductions in density, activity, and metabolism in areas of the brain that come under attack in late-onset Alzheimer’s disease (AD), scientists at Brown University and the Banner Alzheimer’s Institute have gone back even earlier in time to study infants. They reported that babies as young as six months born with the AD risk gene are already showing significant brain differences compared with those born without a copy of the APOE4 gene.

The study, published in the Nov. 25 online edition of the Journal of the American Medical Association Neurology (JAMA Neurology), raises questions about APOE’s role in Alzheimer’s disease.

A Neuroscientist’s Quest to Treat Lennox-Gastaut Syndrome — in Her Daughter

BY THOMAS R. COLLINS

Tracy Dixon-Salazar, PhD, held her audience captive last October when she took to the lectern for a featured plenary at the American Neurological Association annual meeting. The associate research director at Citizens United for Research in Epilepsy (CURE) had come to talk about her research at the University of California, San Diego (UCSD), which had led to the identification of gene abnormalities in a patient with Lennox-Gastaut syndrome, a form of epilepsy that starts in childhood. And she had encouraging news — treatment with a calcium-channel blocker had reduced seizures in that patient from 300 a month to 20.
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measurement of the health of the white matter and degree of myelination — in 60 APOE4 carriers and 102 non-carriers, and gray matter volume (GMV) in 23 APOE4 carriers and 36 non-carriers.

The infants with at least one copy of APOE4 had lower WMV and GMV in precuneus, posterior/medial cingulate, lateral temporal, and medial occipitotemporal regions compared with non-carriers. These regions are preferentially vulnerable in AD. They also reported greater WMV and GMV measurements in discrete frontal regions.

Eric Reiman, MD, executive director of the Banner Alzheimer's Institute in Phoenix, AZ, and one of the study's senior authors, said, "The findings should be considered preliminary," but the study "demonstrates some of the earliest brain changes associated with the genetic predisposition to Alzheimer's."

Dr. Reiman and his Arizona colleagues first identified reductions in glucose metabolism in brain regions affected by AD in young adults carrying an APOE4 allele, and it did not accelerate between the third and fifth decade. They suggested in a 2004 study in the Proceedings of the National Academy of Sciences that these were developmental changes and could portend vulnerability to the disease. They went on to extend their findings to post-mortem brain tissue from young adults.

Dr. Reiman met members of the Brown's Advanced Baby Imaging Laboratory during a visit to Brown. They were conducting neurodevelopmental studies on normal infants and young children. He asked if his Arizona colleagues could characterize the children's APOE genotypes and work with them to compare brain images in the APOE4 carriers and non-carrier groups.

"Our findings raise more questions than answers," said Dr. Reiman. "Additional studies are needed to clarify the neurodevelopmental processes affected by APOE variants, the extent to which these or other neurodevelopmental processes provide a foothold for the pathogenesis of Alzheimer's in older adults, and the extent to which these processes could be targeted in the discovery of treatments to prevent this disease."

While it is possible to know the underlying substrates responsible for these brain differences, Dr. Reiman has some thoughts about the mechanism. APOE is involved in white matter myelination, maintaining and repairing myelin and the E4 allele makes the system less efficient, Dr. De Dena added.

One of the lead authors of the study, Douglas C. Dean III, PhD, of Brown University's School of Engineering, heads up the ongoing study of normal development at Brown's Advanced Baby Imaging Laboratory.
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Lab. The investigators have recruited around 400 children, and now have amassed information from 700 brain scans. They have mined the data to study the role of breastfeeding on early brain development, are studying language acquisition, and are conducting a broad range of cognitive and behavioral assessments on the children over time.

"While our findings may have implications for the scientific study of Alzheimer's disease, they do not yet have any clinical implications. Brain scans and APOE genotypes are not clinically indicated to determine a healthy child's risk for learning disabilities or the clinical onset of AD at older ages," said Dr. Reiman.

"These results do not establish a direct link to the changes seen in Alzheimer's patients, but with more research they may tell us something about how the gene contributes to Alzheimer's risk later in life," added Dr. Deoni.

EXPERTS WEIGH IN

"The study is clever and the finding are intriguing," said Bradley T. Hyman, MD, PhD, the John B. Penney, Jr. professor and director of the Alzheimer's Disease Research Center at Massachusetts General Hospital. Dr. Hyman and John H. Growdon, MD, director of the Movement Disorders Unit at Massachusetts General Hospital, wrote an accompanying editorial in JAMA Neurology.

"We've had evidence that there are already differences by middle-age," Dr. Hyman told Neurology Today in a telephone interview. "When does it start becoming different? Is this a fundamental developmental issue or is it related to Alzheimer's? We just don't know."

The brain changes - low metabolic activity in areas hard-hit in AD — in young and middle-aged adults with APOE4 suggested that there is a long prodromal period before the onset of obvious clinical signs. "But this latest study tells us that there is more to it than that," said Dr. Hyman. "APOE4's role in early development may make the brain somewhat more vulnerable later in life."

"It is hard to interpret [if its] better or worse when you look at these changes," Dr. Hyman added. "That the brains are different is the take-home message. It is hard to know what it all means." He said that studies on adults have been done that suggests that APOE genotype does not affect average intelligence. "Something else must be going on," said Dr. Hyman.

John C. Morris, MD, director of the Charles F and Joanne Knight Alzheimer's Disease Research Center at Washington University, noted that the study authors were careful to call the findings preliminary. "It is provocative," he said. "It will be important for future studies to extend this finding and try to understand its relationship to the genetic factors at work in Alzheimer's."

"Studies have shown that adults with APOE4 have metabolic changes. This study pushes things back even further and says that APOE4 as a risk factor may be operating over a lifetime. We are interested in genetic risk factors and how these risk factors interact with the greatest AD risk factor of all — aging."

"There are clearly differences in brain function in E4 carriers," said John Hardy, PhD, a professor of neuroscience and Movement Disorders Unit at University College London, and an expert in Alzheimer's. "That the brains are somewhat more vulnerable later in life."

"So what does it mean? "I really don't know," said Dr. Knopman. "It is a really important question. An attractive idea is that APOE is involved in regulation of cellular energy metabolism and that the E4 allele promotes a less efficient pathway for ATP production. The only way I know to relate this to AD is that the regions affected have the highest energy demands of any brain region. But this is utter speculation." It will be important for colleagues to figure out the links between APOE4, development, aging and AD. Dr. Knopman said. Still, he added, "hypo-metabolic changes probably do constitute a risk for AD," and investigators will need to figure out what APOE4 is doing to cause changes in the brains of young children.

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DR. JOHN HARDY: "There are clearly differences in brain function in E4 carriers. But that does not mean that it is related to AD. It is interesting and it might be pointing to some function of APOE4 and normal brain development. But we don't know the mechanism for this."

DR. JOHN C. MORRIS: "Studies have shown that adults with APOE4 have metabolic changes. This study pushes things back even further and says that APOE4 as a risk factor may be operating over a lifetime. We are interested in genetic risk factors and how these risk factors interact with the greatest AD risk factor of all — aging."

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