How does traumatic brain injury progress to Alzheimer's disease?

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A traumatic brain injury, or TBI, is caused by a contusion to the head that may result in injury to the brain. This type of injury combined with the inherited genetic risk factors can result in the accelerated...
development of Alzheimer's disease and related dementia, or ADRD.

TBIs range from mild to severe, with the majority being mild. They are especially common in adolescents engaging in contact sports and in the elderly who tend to fall with greater frequency as they age. Regardless of the source, TBI and how it progresses to ADRD is an understudied area of research.

The University of California, Riverside, and Indiana University will examine how TBI at different ages and genetic risk factors lead to ADRD.

"There's some literature that suggests that traumatic brain injury can evolve in some cases to Alzheimer's or accelerate Alzheimer's-like symptoms," said Andre Obenaus, a professor of biomedical sciences at UCR's School of Medicine and principal investigator of the three-year grant.

"We are interested in the complex interplay between TBI and genetic risk factors, and how these increase the susceptibility for individuals to develop Alzheimer's disease and related dementia," said Paul Territo, a professor of medicine at the Indiana University School of Medicine, and co-principal investigator of the proposed work.

Using rodents, Obenaus, Territo, and their teams will study three different time periods in the 24-month lifespan of a mouse: the juvenile age, which is postnatal Day 17; midlife, which is when the mice are 8–9 months old; and late life, which is when the mice are 12 months of age. The researchers will use cognitive behavioral outcomes, clinically relevant medical neuroimaging (PET/CT, MRI), immunopathology changes, and tissue biomarkers to assess disease progression.

"This system will allow us to investigate the interactions of how genetics
and TBI in well characterized models across three epochs of lifespan influence progression to ADRD," Obenaus said.

An expert on TBI, stroke, Alzheimer's, and epilepsy, Obenaus has worked on TBI for more than two decades. He joined the UCR faculty in March 2024. He is a member of the consortium, MODEL-AD, tasked with building better models of Alzheimer's disease in mice. The consortium is based at UC Irvine.

Territo, an expert in Alzheimer's disease, biomarker development, and therapeutics testing, has worked in both the academic and pharmaceutical industries developing rigorous and reproducible systems to evaluate disease progression and therapeutic response.

These areas of expertise are extensively leveraged in the MODEL-AD consortium, where his lab characterizes mouse models of ADRD, and then performs therapeutic evaluation of novel drug candidates.

"We hope to identify early on those individual mice that will go on to have an Alzheimer's-like phenotype," Obenaus said.

"We don't expect all the mice to develop Alzheimer's, but a certain subgroup of mice will. The goal is to identify the combinations of risk genes and timing of TBI that modulate fluid and imaging biomarkers involved so that early intervention is possible to prevent, or delay, progression of Alzheimer's."

Medical imaging is the only non-invasive means to assess both TBI and ADRD. When combined with fluid biomarkers, which are biological molecules found in body fluids and tissues, detection of abnormal processes or disease progression is possible.

Obenaus explained that considerable research has been done on TBI, but
scientists still do not fully understand its long-term progression and the biomarkers involved. Territo underscored the combined strength of linking the readouts of medical imaging, immunopathology, and fluid biomarkers into a comprehensive model, which will provide significant improvements in predictive validity in both TBI and ADRD.

"We now have sufficient technical expertise in the field to address this research problem, allowing us to better define TBI and its role in initiating Alzheimer's disease," Obenaus said. "In addition, over the past two decades there has been a wealth of research identifying the two main proteins, tau and amyloid, thought to interfere with the communication between brain cells, and leading to ADRD."

Obenaus and Territo said the data from the research project will be aggregated and made freely available to other researchers through the NIH Open Science framework.

They will be joined in the research project by Adam Godzik and Devin Binder, who are professors of biomedical sciences in the UCR School of Medicine. A research team at the Uniformed Services University of the Health Sciences in Maryland, led by Dr. Denes Agoston, will work on the project as well.

Also joining the team is Talin Babikian, a neuropsychologist at UCLA, who has extensive experience in TBI and its progression. Graduate students and postdoctoral researchers at UCR and Indiana University will also work on the research project.

Provided by University of California - Riverside

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