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Traumatic brain injury may not increase the risk of Alzheimer disease

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ABSTRACT

Traumatic brain injury (TBI) commonly occurs in civilian and military populations. Some epidemiologic studies previously have associated TBI with an increased risk of Alzheimer disease (AD). Recent clinicopathologic and biomarker studies have failed to confirm the relationship of TBI to the development of AD dementia or pathologic changes, and suggest that other neurodegenerative processes might be linked to TBI. Additional studies are required to determine the long-term consequences of TBI. ***Neurology*® 2017;89:1–3**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **PD** = Parkinson disease; **TBI** = traumatic brain injury.

Traumatic brain injury (TBI) is a common injury sustained through military service, sports involvement, falls, or other accidents. The Centers for Disease Control and Prevention reported that in 2013 there were 2.5 million emergency department visits and 282,000 hospitalizations related to TBI in the United States. More than 40% of participants in a recent study reported a lifetime history of either mild or moderate to severe TBI.[1] In active duty US Army members, the overall annual incidence rate of TBI increased from 786 to 2,718 per 100,000 from 2003 to 2011 (cdc.gov/traumaticbraininjury/data/). Increased media coverage of sports and military TBIs has highlighted the profound effect these injuries have on individuals and their families. In addition to short-term cognitive impairment following injury, long-term cognitive functioning is impaired in as many as 65% of patients with moderate to severe TBI.[2] However, the exact nature of the effect on the aging brain has not been well-defined.[3,4]

Alzheimer disease (AD), a β-amyloid (Aβ)–facilitated tauopathy, has been considered a possible pathologic outcome of TBI; amyloid precursor protein, the parent protein of Aβ, is a commonly used immunohistochemical marker of diffuse axonal injury following TBI, especially in white matter[5]; and Aβ has been found in the brains of young decedents following a single severe TBI.[6,7] Therefore numerous epidemiologic studies have examined the link between TBI and AD. The majority of these studies (reviewed in reference 8) reported that TBI elevated the risk for developing AD. Indeed, many ranked TBI only after age, family history, and *APOE* genotype in importance as an AD risk factor.[9] Some reported an interaction between these risk factors: the risk of AD from TBI was higher in carriers of the *APOE* ε4 risk alleles than in noncarriers,[10–14] and higher in male than in female participants. A comprehensive consensus analysis of this literature further bolstered TBI as an AD risk factor, concluding that in men, TBI more than doubled the risk of future development of AD (odds ratio 2.29 [confidence interval 1.47–3.58]).[15]

Almost all epidemiologic studies of the relationship between TBI and AD have 2 major limitations. First, most have used self-report information to determine a history of TBI exposure.

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While the collection of exposure information before the onset of dementia may be a valid approach, collection of exposure data from people who are already cognitively impaired has obvious drawbacks in the reliability of the data. Second, most studies have relied on billing codes for clinical diagnosis of AD dementia rather than using an array of recently developed biomarkers or neuropathologic examination.

These limitations were overcome in 2 recent studies examining the relationship between TBI and AD. In one report, the self-reported TBI, with more than 1 hour loss of consciousness, was collected at a time when participants were cognitively intact. The late effects of this TBI were investigated in 3 large community-based cohort studies on brain aging and dementia—the Religious Orders Study, the Memory and Aging Project, and the Adult Changes in Thought study—that ask participants to donate their brains for research.[16] Of 7,130 participants, 1,589 underwent brain autopsy over the 20-year period from 1994 to 2014. This report focused on the spectrum of common age-related diseases of the brain including AD, vascular brain injury, hippocampal sclerosis, and Parkinson disease (PD) and its pathologic hallmark, Lewy body disease. Pooled analysis showed that a history of TBI with loss of consciousness was not associated with AD dementia or the neuropathologic features of AD; rather it was associated with Lewy body disease, PD, and progression of parkinsonism. Unlike some epidemiologic studies, well-powered analyses did not find interactions between clinical or neuropathologic AD outcomes for TBI and the *APOE* ε4 genotype or sex.

A second report used Veterans Administration medical records to document a history of TBI and established AD biomarkers to measure AD pathology. The study investigated the extent to which a history of TBI increases the odds of developing cognitive impairments or changes in AD biomarkers, which included structural brain changes on MRI and Aβ deposition measured by florbetapir PET scans. The results showed no effects of TBI history on cognition or AD biomarkers.[17]

These data fail to support TBI as a risk factor for developing AD dementia. Both studies circumvented the limitation of self-reported TBI in cognitively impaired participants—one used self-reported TBI with loss of consciousness collected at a time when participants were known to be cognitively intact,[16] and the other used medical records information to document TBI exposure.[17] Likewise, neither study relied solely on clinical diagnosis of dementia and AD, but augmented diagnosis with neuropathology evaluations[16] or MRI and florbetapir PET scans.[17]

These large, well-powered, and carefully conducted studies cast substantial doubt on the association between TBI exposure and AD outcomes, both overall and among men and carriers of *APOE* ε4 alleles. What then are the long-term implications of TBI exposure? The association of TBI with PD neuropathology[16] suggests that TBI exposure is not innocuous and is consistent with a recent large epidemiologic study that found an increased risk of PD following late life TBI.[18] Neuropathologic outcomes appear to differ depending on the severity or frequency of the TBI.[4] Further investigation is clearly needed to determine the relationship of TBI to cognitive decline in the elderly in order to effectively address this serious public health problem.

AUTHOR CONTRIBUTIONS

Dr. Weiner: view concept, critical revision of manuscript for intellectual content. Dr. Crane: view concept, critical revision of manuscript for intellectual content. Drs. Montine and Bennett: view concept, critical revision of manuscript for intellectual content. Dr. Veitch: drafting and revision of manuscript.

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