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Traumatic Brain Injury May Increase Risk of Young Onset Dementia

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Since 1906, when Alois Alzheimer first described the clinical and pathological features of Alzheimer disease (AD) in a 51-year-old woman,¹ our understanding of the clinical subtypes, underlying pathologies, pathophysiologicals, and risk factors for dementia has increased tremendously. By 1928, an astute pathologist reported a unique type of dementia associated with repeated traumatic brain injury (TBI) in boxers.² A history of exposure to TBI has subsequently emerged as an important risk factor for dementia in older adults in many,^{3–9} but not all,^{10,11} epidemiological studies and meta-analyses. The contribution of TBI to young onset dementia (YOD), defined as dementia before age 65 years, has not been as thoroughly investigated. This gap is partly due to the challenges of designing a study of dementia in a population with a relatively low incidence of this outcome. The exposure rate to TBI in this population, however, is quite high. In the United States alone, TBI accounts for an estimated 1.4 million emergency department visits annually in patients younger than 65 years.¹² Given the number of patients who suffer TBI and do not seek medical attention, this is likely a gross underestimate of the actual exposure rate.¹³ Thus, even a small increased risk of dementia in the population of TBI-exposed young adults could have important public health implications.

In this issue of *Annals of Neurology*, Nordstrom et al¹⁴ report the results of a Swedish epidemiological study evaluating the risk of YOD after TBI in a cohort of >800,000 young men (>45,000 with TBI) followed for >3 decades. This study may be the first of its size to address this important question in a dedicated fashion. The authors report a strong dose–response association between TBI and all-cause YOD, such that more severe or frequent TBI is associated with an ever-increasing risk of all-cause YOD. After adjustment for covariates, this association and dose–response effect were attenuated, but remained significant, with a hazard ratio (HR) of 1.5 for mild TBI and 2.3 for severe TBI. In a secondary nested case–control sensitivity analysis, in which the authors used propensity score matching, the risk was even greater (HR = 1.8 for mild TBI; HR = 2.9 for severe TBI). This study has many strengths, including novelty, clinical importance, and methodological

Potential Conflicts of Interest

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rigor. The authors employed physician-generated diagnoses of TBI, thus eliminating potential recall bias that has limited many prior studies of this topic, but missing cases that did not come to medical attention. They also included many important covariates such as baseline cognitive status, thus strengthening causality following multivariable adjustment.

National databases of administrative health data present a wealth of opportunities for epidemiological research due to the sheer size of the cohorts and to the availability of long-term follow-up in many cases. These studies, however, must be interpreted in the context of potential coding idiosyncrasies—both by the providers assigning codes to the patients during an encounter and by the researchers selecting the codes to include in the study definitions. In their study, Nordstrom et al employ a TBI stratification scheme that differs from that recommended by the Centers for Disease Control and Prevention¹⁵ and implemented by many prior studies. Although this approach may limit direct comparison to prior studies, the authors' sensitivity analysis of mortality after TBI, as well as the persistence of a dose response after adjustment for covariates, supports the clinical validity of their stratification scheme. The authors also stratified by dementia subtypes, distinguishing between AD and non-AD dementia. It is well known that general practitioners often under- or misreport dementia subtypes, potentially leading to underidentification of cases of AD within the AD cohort. Only 14 cases of AD were identified among the TBI-exposed subjects, resulting in limited power. We therefore caution readers against overinterpretation of dementia subtype results and encourage readers to focus on results for the analysis of "all cases of dementia."

Leading theories of mechanisms whereby TBI may increase risk of dementia include reduction of cognitive reserve, augmentation of incipient neurodegenerative processes, and initiation of de novo neurodegenerative processes. Although the precise underlying pathophysiological mechanisms are being investigated, there is a growing body of basic and translational research that lends support to a causal link between TBI and neurodegenerative disease. At the time of a nonpenetrating TBI, mechanical forces exerted on brain tissue may produce multifocal axonal shear injuries, which have been shown in animal studies to lead to immediate changes in axonal membrane permeability, massive calcium influx, and release of caspases and calpains that have been implicated in subsequent abnormal protein phosphorylation and aggregation.^{16–19} Human studies of acute TBI have revealed axonal accumulation of a number of abnormal proteins, including tau, amyloid-beta, and alpha-synuclein,²⁰ that are implicated in a range of different neurodegenerative diseases, including chronic traumatic encephalopathy, AD, frontotemporal dementia, and Parkinson disease. Many of these abnormal proteins are known to self-propagate via cross-seeding and neuron-to-neuron transfer mechanisms,^{21–26} which may then seed functionally connected neuronal networks,²⁷ thereby triggering a more widespread neurodegenerative cascade. Based on these proposed mechanisms, it stands to reason that TBI may be associated not only with late onset dementia, but also with YOD, particularly in patients with other risk factors that may promote the initiation and propagation of this cascade. For example, apolipoprotein E epsilon 4 has been shown to reduce the brain's ability to recover post-TBI,²⁸ and TBI sustained in childhood or adolescence may be more morbid than TBI sustained later in life.^{29,30} The lack of dementia in many TBI-exposed individuals, however, indicates that post-TBI neurodegeneration is a multifactorial process that is likely dependent upon

number, mechanics, and timing of TBIs, individual genetics, and many other health-related, lifestyle, and environmental risk and protective factors.

Overall, this is an important study by Nordstrom et al that addresses an understudied question and raises the possibility that mild or severe TBI may increase risk of YOD. As the authors point out, this is a topic that requires further examination in large prospective longitudinal studies ending in autopsy, which will inform development of diagnostic, treatment, and prevention strategies.

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References

1. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde." Clin Anat. 1995; 8:429–431. [PubMed: 8713166]
2. Martland HS. Punch drunk. JAMA. 1928; 91:1103–1107.
3. Mortimer JA, French LR, Hutton JT, Schuman LM. Head injury as a risk factor for Alzheimer's disease. Neurology. 1985; 35:264–267. [PubMed: 3969219]
4. Graves AB, White E, Koepsell TD, et al. The association between head trauma and Alzheimer's disease. Am J Epidemiol. 1990; 131:491–501. [PubMed: 2405648]
5. Molgaard CA, Stanford EP, Morton DJ, et al. Epidemiology of head trauma and neurocognitive impairment in a multi-ethnic population. Neuroepidemiology. 1990; 9:233–242. [PubMed: 2087247]
6. Salib E, Hillier V. Head injury and the risk of Alzheimer's disease: a case control study. Int J Geriatr Psychiatry. 1997; 12:363–368. [PubMed: 9152722]
7. Guo Z, Cupples LA, Kurz A, et al. Head injury and the risk of AD in the MIRAGE study. Neurology. 2000; 54:1316–1323. [PubMed: 10746604]
8. Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000; 55:1158–1166. [PubMed: 11071494]
9. Lee YK, Hou SW, Lee CC, et al. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. PloS One. 2013; 8:e62422. [PubMed: 23658727]
10. Katzman R, Aronson M, Fuld P, et al. Development of dementing illnesses in an 80-year-old volunteer cohort. Ann Neurol. 1989; 25:317–324. [PubMed: 2712531]
11. Dams-O'Connor K, Gibbons LE, Bowen JD, et al. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. J Neurol Neurosurg Psychiatry. 2013; 84:177–182. [PubMed: 23172868]
12. Faul M, Xu L, Wald MM, et al. Traumatic brain injury in the United States: national estimates of prevalence and incidence, 2002-2006. Inj Prev. 2010; 16:A268–A.
13. Setnik L, Bazarian JJ. The characteristics of patients who do not seek medical treatment for traumatic brain injury. Brain Inj. 2007; 21:1–9. [PubMed: 17364514]
14. Nordström P, Michaëlsson K, Gustafson Y, Nordström A. Traumatic brain injury and young onset dementia: A nationwide cohort study. Ann Neurol. 2014; 75:000–000.
15. National Center for Injury Prevention. Mild traumatic brain injury in the United States: steps to prevent a serious public health problem. Centers for Disease Control and Prevention; Atlanta, GA: 2003. Report to Congress.

16. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train.* 2001; 36:228–235. [PubMed: 12937489]
17. Binder LI, Guillozet-Bongaarts AL, Garcia-Sierra F, Berry RW. Tau, tangles, and Alzheimer's disease. *Biochim Biophys Acta.* 2005; 1739:216–223. [PubMed: 15615640]
18. Serbest G, Burkhardt MF, Siman R, et al. Temporal profiles of cytoskeletal protein loss following traumatic axonal injury in mice. *Neurochem Res.* 2007; 32:2006–2014. [PubMed: 17401646]
19. Geddes JF, Vowles GH, Nicoll JA, Revesz T. Neuronal cytoskeletal changes are an early consequence of repetitive head injury. *Acta Neuropathol.* 1999; 98:171–178. [PubMed: 10442557]
20. Uryu K, Chen XH, Martinez D, et al. Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. *Exp Neurol.* 2007; 208:185–192. [PubMed: 17826768]
21. Le MN, Kim W, Lee S, et al. Multiple mechanisms of extracellular tau spreading in a non-transgenic tauopathy model. *Am J Neurodegener Dis.* 2012; 1:316–333. [PubMed: 23383401]
22. Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. *J Biol Chem.* 2009; 284:12845–12852. [PubMed: 19282288]
23. Johan K, Westermarck G, Engstrom U, et al. Acceleration of amyloid protein A amyloidosis by amyloid-like synthetic fibrils. *Proc Natl Acad Sci U S A.* 1998; 95:2558–2563. [PubMed: 9482925]
24. Morales R, Estrada LD, Diaz-Espinoza R, et al. Molecular cross talk between misfolded proteins in animal models of Alzheimer's and prion diseases. *J Neurosci.* 2010; 30:4528–4535. [PubMed: 20357103]
25. Freundt EC, Maynard N, Clancy EK, et al. Neuron-to-neuron transmission of alpha-synuclein fibrils through axonal transport. *Ann Neurol.* 2012; 72:517–524. [PubMed: 23109146]
26. Hansen C, Li JY. Beyond alpha-synuclein transfer: pathology propagation in Parkinson's disease. *Trends Mol Med.* 2012; 18:248–255. [PubMed: 22503115]
27. Seeley WW, Crawford RK, Zhou J, et al. Neurodegenerative diseases target large-scale human brain networks. *Neuron.* 2009; 62:42–52. [PubMed: 19376066]
28. Crawford F, Wood M, Ferguson S, et al. Apolipoprotein E-genotype dependent hippocampal and cortical responses to traumatic brain injury. *Neuroscience.* 2009; 159:1349–1362. [PubMed: 19409232]
29. Field M, Collins MW, Lovell MR, Maroon J. Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. *J Pediatr.* 2003; 142:546–553. [PubMed: 12756388]
30. Pulella R, Raber J, Pfankuch T, et al. Traumatic injury to the immature brain results in progressive neuronal loss, hyperactivity and delayed cognitive impairments. *Dev Neurosci.* 2006; 28:396–409. [PubMed: 16943663]