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Traumatic brain injury

Age at injury influences dementia risk after traumatic brain injury

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Traumatic brain injury (TBI) is increasingly recognized as a risk factor for dementia. New data provide further support for this association, and demonstrate the influence of age at injury and injury severity on dementia risk post-TBI; revealing that even mild TBI increases dementia risk in those aged ≥ 65 years.

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The association between traumatic brain injury (TBI) and increased risk of dementia has garnered intense public and media interest in the past few years. In a newly published, comprehensive study of 164,611 patients with trauma aged ≥ 55 years at the time of injury, the strength of this association is explored further¹; the results highlighting the influence of age on dementia risk following a TBI. In support of previous work, Gardner and colleagues¹ report an increased dementia risk following a single moderate to severe TBI across their patient cohort at up to 7 years of follow-up. Furthermore, an intriguing aspect of the analysis indicates that even a single, mild TBI might confer increased dementia risk in older patients; defined as those aged ≥ 65 at the time of injury. Thus, the implications of this study are that risk of neurodegeneration after TBI is influenced not just by the severity of the initial injury, but also by the patient's age at the time of injury.

In the past 5 years considerable attention has been paid to the link between repetitive, mild TBI and neurodegenerative disease. This interest has, in large part, been driven by increasing reports of chronic traumatic encephalopathy (CTE) in autopsy studies of former athletes or military personnel.^{2,3} However, the association between exposure to a single moderate or severe TBI and increased risk of dementia has been recognized for some time. Characterization of autopsy acquired material from long-term survivors of a single TBI reveals a complex neuropathology in a proportion of patients. This complex neuropathology, best described as a 'poly pathology', includes abnormal tau and amyloid- β protein accumulation,⁴ neuroinflammation, white matter degradation and axonal degeneration,⁵ adding further to our appreciation of the full range of CTE pathology. However, although the neurodegenerative pathology of TBI is increasingly understood, conflicting reports exist regarding the epidemiological association of a single TBI with altered risk of dementia, which might reflect methodological limitations of studies on both sides of this debate.⁶

Several previous clinical studies have used a methodology comparing incidence of dementia in patients with TBI to that of the general population. In the new study by Gardner *et al.*¹ a more relevant index population of over 112,000 patients exposed to trauma without TBI provides the 'control' population. Over a follow-up period of up to 7 years after the original injury dementia risk in a cohort of almost 52,000 patients with TBI was assessed in comparison to this cohort of

patients exposed to trauma without TBI. As such, the authors attempted to mitigate against potentially unknown behavioural or clinical confounders that might also confer an increased risk of dementia in patients exposed to trauma.

Rather than relying on self or informant reporting of dementia, only confirmed, hospital-based diagnoses (International Classification of Diseases, Ninth Revision coded) were used to determine dementia outcome at follow-up. Importantly, patients in which a diagnosis of dementia was made within 1 year following injury were excluded from the analysis. This criterion reduced the possibility that pre-existing dementia acting as a risk factor for trauma, or evolving subacute TBI pathology might confound dementia diagnosis. Using this methodology, and adjusting for all covariables, the data are reported to show an increased dementia risk in patients surviving TBI compared with patients with trauma, without TBI across all age groups studied.

Intriguingly, this study also reveals a potential association between age at injury, injury severity and subsequent risk of dementia. The data demonstrate increased dementia risk following either a moderate, or severe TBI across the cohort. However, in the older patients in this study, defined as those aged e65 at time of injury, just a single, mild TBI was sufficient to increase dementia risk. Notably, TBI is a major public health problem in older individuals, with the highest rates of hospitalization from TBI observed in those aged e65.⁷

Research has resulted in an increased appreciation of the range of neuropathologies associated with “normal” ageing, which show overlap with pathologies typically associated with neurodegenerative diseases, including brain atrophy, neurofibrillary tangles and amyloid- β plaques.⁸ To avoid the confounding influence of ‘normal’ ageing, many studies investigating TBI-associated neurodegenerative pathologies often exclude older individuals and focus on younger patients. However, the study by Gardner *et al.*¹ underlines the pressing need to further examine the interplay between TBI, age and dementia risk. The presence of comorbidities, and their potential contribution to pathophysiology is of particular relevance in this older age group. In this respect, the population of patients with TBI in this study was slightly older, had a higher percentage of males and a higher incidence of cardiovascular comorbidities than the counterpart cohort of patients with trauma without TBI. While the association with dementia risk remained after adjustment for these covariates, the need for robust accounting for comorbidities is critical to further investigation of the potential mechanisms of disease, particularly in mild TBI.

Owing to the inherent restrictions of retrospective analyses, one limitation of this work is the inability to exclude previous TBIs that might have occurred prior to the period of study, including repetitive mild exposures. To date, the association between repetitive mild TBI and chronic neurodegeneration has not been robustly explored at a population level, with the vast majority of data being derived from relatively small and highly-selective case series.^{2,3} As such, any

speculation as to how this potential variable might influence dementia risk is limited. However, Gardner *et al.*¹ did note that patients with a second TBI during follow-up had twice the dementia risk, suggesting a dose-response relationship.

Overall, this work represents an important contribution to our understanding of the association between TBI and increased risk of dementia. These findings also underscore the pressing need for further, well-constructed, longitudinal studies examining the chronic and progressive consequences of TBI across all age groups. Risk of a worse outcome in the acute period following TBI is known to increase with older age.^{9,10} Given the advancing average age observed in many national populations, further understanding of any age-associated vulnerability to progressive neurodegenerative outcomes following TBI will be of critical importance.

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1. Gardner, R. C., *et al.* Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol.* <http://dx.doi.org/10.1001/jamaneurol.2014.2668>.
2. McKee, A. C., *et al.* The spectrum of disease in chronic traumatic encephalopathy. *Brain* **136**, 43–64 (2013).
3. Smith, D. H., Johnson, V. E. & Stewart, W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat. Rev. Neurol.* **9**, 211–221 (2013).

4. Johnson, V. E., Stewart, W. & Smith, D. H. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. *Brain Pathol.* **22**, 142–149 (2012).
5. Johnson, V. E., *et al.* Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* **136**, 28–42 (2013).
6. Fleming, S., *et al.* Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J. Neurol. Neurosurg. Psychiatry* **74**, 857–862 (2003).
7. Faul, M., Xu, L., Wald, M. M. & Coronado, V. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002–2006. Centers for Disease Control and Prevention [online] http://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf. (2010)
8. Savva, G. M., *et al.* Age, neuropathology, and dementia. *N. Engl. J. Med.* **360**, 2302–2309 (2009).
9. Susman, M., *et al.* Traumatic brain injury in the elderly: increased mortality and worse functional outcome at discharge despite lower injury severity. *J. Trauma* **53**, 219–223 (2002).
10. Hukkelhoven, C. W., *et al.* Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *J. Neurosurgery* **99**, 666–673 (2003).

Figure 1: Influence of age, and injury severity on neurodegeneration following TBI. The neurodegenerative pathologies described in TBI survivors might also arise through 'normal' ageing (black line). The data presented by Gardner *et al.*¹ support the hypothesis of an accelerated accumulation of neurodegenerative pathology following a single moderate or severe TBI (red line), so crossing a threshold to clinical symptoms (dotted line) at an earlier age. In contrast, increased dementia risk after mild TBI was only present in patients aged ≥ 65 (orange line), implying no meaningful acceleration in neurodegenerative pathologies in patients aged <65 (blue line). Abbreviation: TBI, traumatic brain injury. Modified with permission obtained from Nature Publishing Group © Smith, R. M. *et al.* Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat. Rev. Neurol.* **9**, 211–221 (2013).

...even a single, mild TBI might confer increased dementia risk in older patients...

...Gardner and colleagues¹ report an increased dementia risk following a single moderate to severe TBI...

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