
Traumatic Brain Injury and Dementia

As Canada's population ages, the incidence of traumatic brain injury (TBI) and the prevalence of dementia will certainly increase. Dementia is a significant risk factor for the two most common causes of brain injury, namely falls and motor vehicle accidents. TBI is associated with a variety of cognitive deficits and may lead to the development of dementia. There is now compelling data to suggest that TBI causes AD.

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While traumatic brain injury (TBI) is most commonly seen in adolescents and young adults, there is a bimodal distribution with a second peak in incidence after the age of 65 years.¹ In Canada, unintentional injuries were the sixth-leading cause of death (22.8 deaths per 100,000 population) among adults aged 65 years and older in 1996/1997.² Among the causes of these injuries, falls and motor vehicle collisions were the most common causes of death and

hospitalization.² TBI is the third-most common injury leading to hospitalization in older adults.³

In Canada, an estimated 8% of the population has dementia and a further 16.8% have cognitive impairment without dementia.⁴ Alzheimer's Disease (AD) is the most common cause of dementia in older adults.^{5,6} As of 1992, 364,000 Canadians over the age of 65 years had AD and related dementias, and it has been estimated that, by 2021, this figure will reach 592,000.⁷ As persons over the age of 65 years represent the fastest-growing segment of the Canadian population, and are expected to comprise 25% of the total population by the year 2030,⁷ it will become increasingly important to prevent TBI and AD whenever possible.

For the purposes of this paper, we will first explore dementia as a risk factor for TBI and then discuss evidence that suggests that TBI may cause dementia. This paper will discuss the relationship between TBI and dementia, using Sir Bradford Hill's criteria⁸ for the establishment of an argument

of causation. As reviewed by Dr. van Reekum,⁹ the most important of these criteria require that: a) the causal agent and the purported outcome be associated; b) the causal agent should come first; and c) it should be biologically plausible that the putative causative agent might cause the purported outcome.

Dementia as a Risk Factor for TBI

The two most common causes of TBI in the elderly are motor vehicle accidents and falls. Dementia is an important risk factor for both of these.

Driving. An estimated 4% of male drivers aged 75 years and older have dementia,¹⁰ although in an older study of a retirement community, 18% of drivers aged 60 years and older were found to have "senility."¹¹ While incident dementia is a common reason for driving cessation, between 22% and 68%^{10,12,13} of dementia patients continue to drive, and about one third of patients with dementia have at least one motor vehicle collision before ceasing to

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drive.¹²⁻¹⁴ Crash rates in dementia are increased two to eight times relative to age-matched controls.^{14,15} Research generally supports the notion that patients with dementia have higher crash rates and perform more poorly during on-road or simulator assessments, but there are many exceptions.^{16,17} Cognition itself, however, only captures some elements of driving risk. Cognitive screening tests, such as the Mini-Mental Status Examination (MMSE), have limited utility in predicting driving performance in mild dementia.¹⁷⁻¹⁹ Furthermore, more detailed neuropsychological tests, which are not readily available in the community, predict only 19% of the variance of collisions.²⁰ Other factors, such as comorbid health problems and medication use, may play a significant role.

Falls. In a cross-sectional survey of emergency-room patients presenting with falls, dementia was seen as a strong risk factor for falls in the previous 12 months with an odds ratio of 3.80.²¹ Similarly, a recent prospective cohort study in a chronic-care setting found dementia to be a strong predictor of the risk of falls. The risk of falling is double for those with dementia compared to those without.²² Analogous results were found in a cross-sectional analysis of patients discharged from medical inpatient services.²³

The studies above describe an association between a causative agent (i.e., dementia) and an outcome (i.e., falls or motor vehicle collisions) in which the causative agent comes first. Decline in attention, visuospatial skills, and

psychomotor speed associated with dementia provide a feasible biological mechanism that puts such patients at risk of injury. While clearly not all falls or collisions lead to TBI, they are the most common causes of TBI and represent a means by which TBI may be prevented in the dementia population. Clearer institutional and governmental policies are needed to provide guidance on which patients with dementia should not be allowed to drive and

measures must be put in place to prevent falls in chronic-care or ambulatory patients with dementia.

TBI as a Cause of Dementia Cognitive sequelae of TBI.

Cognitive sequelae are among the most disabling of post-concussion symptoms following TBI²⁴ and typically contribute more to persisting disability than physical impairment.²⁵ Following TBI, deficits are consistently demonstrated in the domains of attention,²⁶ memory^{27,28} and executive functioning.^{29,30} To date, there are few studies of cognitive outcome following TBI in the elderly, and these have generally had small sample sizes or have lacked a control group.³¹ A recent report indicated that patients with mild TBI were similar in terms of cognition to matched controls in the first months after injury, and that only patients with moderate TBI

demonstrated deficits.³² Another study showed no difference in cognition six weeks post-injury between older patients with TBI and orthopedic controls.³³ Longer-term studies with larger sample sizes are needed to further elucidate the effects of TBI on cognition in the elderly.

Dementia. Results of a recent meta-analysis³⁴ of 15 of the available and methodologically rigorous case-control studies show that TBI is associated with

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AD, at least in males (odds ratio of 2.3 for males, and of 0.9 for females). The absence of an association in females may relate to protective effects of estrogen, or to other differences in female vs. male neuroanatomy/physiology, or may relate to differences in the nature of the accidents which cause TBI in males vs. females, or perhaps to other factors not yet understood. As reviewed by Dr. Rapoport,³¹ the association between TBI and AD has not been found consistently between studies, with, for example, a relative risk of 4.1 found in one prospective cohort study³⁵ and an absence of increased relative risk found in another.³⁶ An historical cohort study³⁷ found an association between TBI and AD, not in terms of increased frequency of AD but rather in terms of earlier onset of AD (median 10 years

from the date of the TBI vs. an expected 18 years based on age of onset distributions). Finally, evidence of an association between AD and TBI exists at the pathological level as well.³⁸ Of 58 consecutive autopsies performed on individuals (mean age 77.0 years), who had suffered a severe TBI, 22.4% had definite or probable AD based on Braak staging of Alzheimer's pathology vs. 14% in the general population older than age 70 years. Note that there is evidence that even mild TBI (or concussions) may be associated with AD.^{34,39,40}

Common pathologies. The temporal sequence frequently appears to be correct^{31,34,35,37,38} in that both the case-control and

cerebrospinal A_β-peptide levels in humans who have suffered a severe TBI;⁴³

iv) cause mild atrophy of the hippocampus⁴⁰ in mice who have had a single mild TBI (the atrophy is severe in apo-E-deficient mice, suggesting an interaction with apo-E); and

v) cause glial protein immunoreactivity⁴⁰ in these same mice (which is also worse in apo-E-deficient mice).

Another theory is that TBI does not cause AD but rather that, by destroying neurons, TBI reduces the critical reserve of neurons and hence hastens the onset of AD.⁴⁴ Finally, a review⁴⁵ of limited data has suggested that

major depression is common following TBI,⁴⁸⁻⁵⁰ it may interact with the TBI itself to perpetuate the cognitive disturbance.

ii) The epsilon 4 allele of apolipoprotein E (apoE-ε4) has been established as a genetic risk factor for AD, but may also predict poor functional^{51,52} outcome following TBI. While one short-term study found that the presence of apoE-ε4 was associated with memory deficits post TBI,⁵³ a recent study with long-term neuropsychological data failed to demonstrate a relationship between apoE-ε4 and cognition.⁵⁴ Nonetheless, apoE-ε4 appears to interact with the TBI in predicting the development of AD.³¹ In about 30% of severe TBI patients, beta-amyloid protein deposits were observed post-mortem in one or more brain areas.⁵⁵ The beta-amyloid protein deposition post-TBI is strongly, and probably synergistically, enhanced by the presence of the apoE-ε4 allele.⁵⁶⁻⁵⁹ The beta-amyloid protein is, at least initially, mainly deposited as diffuse rather than dense core plaques.^{55,60-62}

iii) The elderly are commonly affected by an array of medical illnesses and medications, which can affect their cognition. Following a TBI itself, particularly when associated with orthopedic trauma, elderly patients are commonly treated with a number of medications which can lead not only to cognitive impairment, but also to acute delirium.

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cohort studies examined cases in which the TBI preceded the dementing illness. As discussed above, it is clear that the temporal sequence will sometimes occur in the opposite direction (with some individuals with AD having a TBI). In terms of biologic plausibility, TBI has been found to:

- i) affect hippocampal synaptic plasticity⁴¹ in a number of animal studies;
- ii) cause accumulation of amyloid precursor protein in injured axons⁴² with subsequent cleavage to A_β-peptide in rats;
- iii) cause persistent increase in

TBI causes cognitive impairments which are similar to AD, and which interact with the effects of aging to essentially mimic—rather than cause—AD.

Factors Mediating the Relationship Between TBI and Dementia.

Various factors may mediate the relationship between TBI and dementia, as follows:

- i) Major depression has been significantly associated with executive dysfunction⁴⁶ and, in some studies, with deficits in attention⁴⁶ and memory.⁴⁷ As

Conclusions

With the aging of the population, the incidence of TBI and the prevalence of dementia will certainly increase in the years to come. Dementia is a significant risk factor for the two most common causes of brain injury, namely falls and motor vehicle accidents. TBI itself is associated with a variety of cognitive deficits and, over time, may lead to the development of dementia. There is now compelling data to suggest that TBI causes AD, as TBI is associated with an increased risk of developing AD, the temporal sequence is generally correct (with understandable exceptions) and finally because TBI causes changes in the brain that are typical of the pathological changes of AD.

There is now increasing evidence that AD may be prevented,

or at least its onset delayed.⁶³ Clearly, individuals at greater risk are more likely to consider AD prevention and the risks/costs inherent in some of the possible preventive strategies. The TBI population deserves to be made aware of the increase in their level of risk and to be made aware of some of the possible prevention strategies available to them. While further research is required to establish their role, such strategies may include the use of nonsteroidal anti-inflammatories (NSAIDs), vitamin E (and perhaps other antioxidants), control of other risk factors (such as blood pressure and cholesterol/triglycerides) and prevention of further insult to the brain. Maintaining cognitive activities, especially new learning, may also play a preventive role. In the future, there may

well be other, perhaps riskier/costlier, strategies. Public health efforts aimed at preventing collisions in younger adults have thus far targeted alcohol, drunk driving, seatbelts and helmets in their campaigns, while research and policy has lagged behind in investigating health conditions and medications that put older adults at high risk of collision. Falls in older people are multi-factorial and yet a multidisciplinary assessment and treatment program involving exercise and, potentially, home modifications can often prevent these quite effectively.^{64, 65} In the decades to come, it will be increasingly critical to prevent falls and motor vehicle collisions in older adults (and their younger counterparts) as TBI represents a common and preventable cause of cognitive deficits and dementia.

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