A Brief Review of the Research Findings of Increased Risk of Dementia in Association with Traumatic Brain Injury

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In civil law cases provisional damages can be awarded if the disease or deterioration is serious, which means beyond ordinary deterioration and if the risk of disease or deterioration has a measurable chance of occurring. It therefore follows that solicitors' instructions usually require the instructed experts of the field: usually neurologists, neuropsychologists and neuropsychiatrists; to also comment on whether the traumatic brain injury (or other condition involving the brain) may cause any adverse long-term effect.

It is an established finding that brain injury can be associated with an increased risk for epilepsy (Lowenstein, 2009). Research has also found that repeated mild traumatic brain injuries (TBI), such as those experienced by professional boxers, are associated with a high risk of chronic traumatic encephalopathy (CTE), originally termed dementia pugilistica (McKee et al., 2012). It was previously thought that this condition only affected professional boxers, but recent research has found neuropathological features of this condition in retired American football players,

a professional wrestler, a professional hockey player and a soccer player (McKee et al., 2009), as well as in non-athletes (Roberts et al., 1990).

CTE is a type of dementia with distinctive neuropathological features, but clinically it can be mistaken for Alzheimer's disease or fronto-temporal dementia (Gavett et al., 2010, 2011). It usually becomes symptomatic several years after the individual experiences repeated concussive or sub-concussive blows to the head, usually in mid-life (Gavett et al., 2010). Typical clinical features include: disordered cognition, most pronounced for memory and executive skills, disturbances in mood and behaviour, such as apathy and irritability, and Parkinsonian signs (McKee et al., 2012). According to Gavett et al. (2010) probably many individuals could develop CTE following falls, motor vehicle accidents, assaults, epileptic seizures or repeated mild head injuries of diverse origins.

What appears unclear, and therefore controversial, is whether a single (or a few) traumatic brain injuries, such as those sustained in road traffic accidents or assaults, increases the risk of developing dementia later in life. Research in this field has yielded mixed results: several peer-reviewed articles (Dams-O' Connor et al., 2013; Tyas et al., 2001; Williams et al., 1991; Mehta et al., 1999; Ameducci et al., 1986; Launer et al., 1999; Nemetz et al., 1999; Lindsay et al., 2002) have not found a link between TBIs and dementia, while several others have found some kind of relationship between them (Plassman et al., 2000; McKee et al., 2012; Guo et al., 2000; Johnson et al., 2013; Gardner et al., 2014; Johnson & Stewart, 2013 & 2015; Vincent et al., 2014; Shively et al., 2012; Gardner & Yaffe, 2015; Lye & Shores, 2000; Fleminger at al., 2003; Gardner et al., 2015; Godbolt et al., 2014; Johnson et al., 2012).

This article aims at presenting some of the challenges that can make it difficult to conduct research in this field and provides a brief overview of the findings.

Traumatic Brain Injury (TBI)

Brain damage caused by sudden acceleration/deceleration can lead to both focal and diffused lesions, due to the effect of brain rotation. Areas particularly vulnerable to damage are the frontal and temporal lobes, which are involved in executive functioning and memory, as the soft brain accelerates inside the skull and on impact hit the body projections at the base of the skull. Brain rotation can also lead to axonal shearing, where axons can be severely damaged, which causes degeneration of the surrounding brain, commonly named 'diffuse axonal injury' (Hannay et al., 2004). In TBI the brain is affected not only by primary brain injury, but also secondary injury, which can occur as a result of brain swelling, raised intracranial pressure and intracranial bleeding (Hannay et al., 2004). A history of brain injury is a predictor of poor outcome (Thornhill et al., 2000).

Brain injury severity is usually established considering length of post-traumatic amnesia (PTA), score on the Glasgow Coma Scale (GCS) and duration of any loss of consciousness (LoC; Saatman et al., 2008).

Dementia

According to the International Classification of Diseases (ICD-10; WHO, 2001) dementia constitutes a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions. Memory problems are not essential for the diagnosis, but the cognitive profile may help diagnose the type of dementia and therefore the diagnostic process. The ICD-10 reports that consciousness is not clouded in dementia, and that impairment of cognitive function is commonly accompanied and occasionally preceded by deterioration in emotional control, social behaviour or motivation. According to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV; APA, 1994), it is characterised by multiple cognitive deficits, including memory impairment and at least one of the following: aphasia, apraxia, agnosia or disturbance in executive functioning. Social or occupational functioning is also impaired. There is no gross clouding of consciousness, which is usually associated with acute confusional states, such as delirium.

Alzheimer's dementia (AD) is the most common type of dementia; it is a clinical syndrome which has been allocated specific clinical criteria. Criteria suggested by the National Institute of Neurological Disorders and Stroke (NINDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) consider insidious onset and progressive impairment of memory and other cognitive functions as essential.

'Probable' Alzheimer's until autopsy

One of the difficulties in this field of research is that the diagnosis of dementia (and the type of dementia) can only be confirmed at autopsy, and therefore the presence of a number of dementia misdiagnosis is likely.

A moderate or severe TBI is linked to an increased risk of developing not just Alzheimer's dementia (AD) but also Parkinson Disease (PD; Goldman et al., 2006) and Amyotrophic Lateral Sclerosis (ALS; Chen et al., 2007).

It is therefore possible that the kind of dementia that follows repeated head injuries or repetitive mild trauma may be caused by chronic traumatic encephalopathy, alone or in conjunction with other kinds of neurodegenerations (for example, those associated with Alzheimer's disease). Studies that include post-mortem neuropathological verification

provide reliable confirmation of the clinical diagnosis; without this confirmation the prevalence of CTE neuropathological features in the study samples is unknown (Gavett et al., 2010) and it is possible that some of those who have been thought to have developed Alzheimer's dementia have developed (at least concurrently) CTE.

From a clinical point of view, CTE and AD or fronto temporal lobar degeneration can be very similar, although the age of onset for CTE is generally younger than that for AD and the course of the disease is typically slower than that of AD or fronto-temporal lobar degeneration (Gavett et al., 2010).

Jellinger et al. (2001) is one of the few studies that evaluated the risk of Alzheimer's dementia using neuropathological criteria and found that a history of severe traumatic brain injury in individuals with residuals of closed TBI lesions, such as old contusions in the frontal, temporal, or other brain areas (versus no history of brain injury), increased the risk of dementia.

Reliance on self-report or reports from family members vs. review of records

An issue which appears to be affecting the reviewed studies that found no link between TBI and dementia is the reliance on family members or friends to precisely identify whether an individual had sustained a TBI earlier in life.

Personal reports may not be accurate for several reasons including lack of awareness of the brain injury severity (e.g. sometimes individuals who sustained a moderate/severe TBI can report they have had a concussion). Third party reports, such as those by family members could be biased towards remembering TBIs in those individuals who developed dementia, perhaps to try to explain their condition, as well as being affected by potential inaccuracies in relation to the TBI severity.

Another issue is finding the appropriate informant for comparison with a control group, for instance comparing reports from a spouse with reports from a less involved family member.

Different TBI severities grouped together and non-significant results

To complicate matters, studies that showed no link between TBI and dementia included a variety of TBI severities and most often were grouped in one single category for the data analysis, which is likely to have obscured some potentially significant results for the more severe TBIs:

- Launer et al. (1999) and Dams-O'Connor et al. (2013) analysed individuals with self-reported "TBI with loss of consciousness", which could also include mild brain injury.

- Amaducci et al. (1968) and Tyas et al. (2001) included individuals who had been reported by

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relatives (i.e. Amaducci et al., 1968), or whom had self-reported (i.e. Tyas et al., 2001) a "head injury" or "head trauma", which may include not only mild TBIs, but also individuals who might not have sustained any brain injury.

- Williams et al. (1991) analysed medical records to ascertain whether a head trauma had been sustained. They included individuals who had had a "head trauma with presumed brain injury" but no information regarding the usual indicators of TBI severity (e.g. GCS, anterograde and retrograde amnesia) were included.

- Mehta et al. (1999) explored the link between self-reported TBI and dementia. TBIs were grouped into: "loss of consciousness of less than 15 minutes and above 15 minutes", however, the rationale for this is not entirely clear given that a brain injury is usually considered mild with a loss of consciousness of up to 20 (Stein, 1996) or 30 minutes (Kay et al, 1993). This means that this study may have included mild TBIs with moderate and severe TBIs, and it is not clear how many individuals with moderate and severe TBIs participated.

- Lastly, Nemetz et al. (1999) reviewed medical records to include individuals with head trauma and brain involvement: "injury with loss of consciousness, post-traumatic amnesia or neurological signs of brain injury or skull fracture". The inclusion criteria would also be likely to group together TBIs of different severity.

On the other hand, several of the studies finding a link between TBI and dementia also reviewed the medical records:

- Gardner et al. (2014) is one of the few studies that relied on hospital confirmed TBI diagnoses to determine outcome at follow-up and found an increase in dementia risk following a single, moderate or severe TBI. They also found that even a mild TBI contributed to an increased dementia risk in individuals of 65 years of age and older.

- The MIRAGE study (Guo et al., 2000), where information on head injury was collected by interviewing multiple informants and reviewing the medical records, found that individuals who had sustained a head injury with loss of consciousness were 4 times more likely to develop dementia and those who had had a head injury without loss of consciousness were twice as likely.

- Plassman et al. (2000) did not rely on reports, but analysis of the medical records of veterans hospitalised for TBI in midlife (and compared them with veterans hospitalised for other reasons). They found that veterans who had sustained a severe TBI were more than 4 times more likely to develop dementia (compared with a control group) and veterans who had sustained a moderate TBI had double the risk than controls to develop dementia.

Insufficient statistical power due to small sample size and non-significant results

As reviewed above, different studies have employed different designs and had different sample sizes, which may explain their different findings. For instance, the EURODEM re-analysis (Mortimer et al., 1991), in which only cases involving head trauma with loss of consciousness were included, found an association between TBI and dementia when data from seven studies with conflicting results was re-analysed (those with a TBI with loss of consciousness were nearly twice as likely to develop Alzheimer's dementia; Mortimer et al., 1991).

Fleminger at al. (2003) carried out a meta-analysis of 15 studies and estimated that individuals who had sustained a TBI of sufficient severity to cause a loss of consciousness were 50% more likely to develop dementia later in life.

Retrospective vs. Prospective studies

Prospective longitudinal studies of head-injured individuals improve understanding of head trauma as a risk factor for dementia. These involve individuals who have had a TBI and whom were successfully followed-up over time (some individuals may be lost, for instance because they moved away, withdrew from the study or died) and monitored to see how many would go on to develop a dementia. Several prospective longitudinal studies have been published, but future studies should terminate in autopsy to ensure accuracy of diagnosis (standard criteria for CTE alone or mixed CTE and AD may need to be developed).

Retrospective studies, on the other hand, involve gathering information on TBI history in individuals who have been diagnosed with dementia, and as such, are prone to self-recall bias. Individuals, or their family members, who have concerns about perceived memory problems may be more likely to report a history of TBI than those who do not have dementia, however individuals with dementia may have memory problems which can affect their recall of any TBI earlier in life.

It is also difficult to find the appropriate control group to compare individuals who sustained a TBI but who did not develop dementia, taking into account potential variables that could also impact on the likelihood of developing dementia.

Age at the time of injury and injury severity

Most studies that have been reviewed have not considered the relationship between injury severity and when the brain injury was sustained. Gardner et al. (2014) has found these two factors to be relevant. They found that moderate to severe brain injury

sustained after the age of 55 and mild brain injury sustained after the age of 65 is likely to increase the risk of dementia. This risk to develop dementia appears higher if multiple TBI are sustained (Plassman et al., 2000; Smith et al., 2013) and the same has been found for Parkinson's disease (Gardner et al., 2015).

Inter-individual differences

Some studies have found a link between inheritance of an apolipoprotein E4 (ApoEe4) allele and dementia (Mayeux et al., 1995; Mehta et al., 1999; Jordan, 2000), but results have not always been replicated (Guo et al., 2000; Plassman et al., 2000) so this issue remains unclear. Jellinger et al. (2010) carried out neuropathological analysis of brain tissues of 55 individuals (and compared the findings with the analysis of 53 age-matched individuals used as a control group) and found that severe TBI is a risk factor for the development of AD, particularly in subjects lacking the ApoEe4 allele which is considered a risk factor for AD.

Alzheimer's dementia is thought to be due to a mixture of genetic and environmental factors with many variables involved; some modifiable such as high blood pressure and other vascular risk factors, and others unlikely to be affected by lifestyle. However, it is clear that individuals differ in how they respond to a TBI, for instance it is known that not all boxers develop chronic traumatic encephalopathy, so there are likely to be some protective factors in some individuals (Smith et al., 2013).

Gender differences

Only some studies have considered potential gender differences in relation to TBI and dementia risk, which may be due to issue with sample size and statistical power. For instance Jellinger et al. (2010) found no gender differences, but they acknowledge the small sample size may have obscured meaningful differences.

There can also be other variables that interact with gender and dementia risk. Guo et al. (2000) found that the association between head injury and AD was apparent in both men and women, although the relative risk for head injury with loss of consciousness was higher, although not significant, in men than in women.

Plassman et al. (2000) found that younger men who sustained moderate or severe TBI appeared to be at higher risk of developing AD and other dementias later in life, but they could not rule out that other variables (not accounted for in the study) could explain this finding.

On the other hand, Fleminger et al. (2012) found support for the association between TBI and Alzheimer's dementia later in life, but only in males. They recommend carrying out further research using a population based design that relies on medical records to ensure a diagnosis of dementia has been made.

Summary

A traumatic brain injury is not necessary, nor sufficient for the development of dementia; some individuals develop dementia without a history of head injury and others who sustain a brain injury may not go on to develop dementia.

Emerging evidence suggests that moderate and severe TBI are a risk factor for dementia (although age at injury appears to be an important factor). Mild TBI may also be linked to an increased risk if sustained later in life. A TBI however appears to be only one of many risk factors. For instance high cholesterol, obesity high blood pressure and diabetes are risk factors in case of Alzheimer's and vascular dementia (Qiu, 2012). Environmental factors, such as toxins, have been found to be implied in some neurological progressive conditions, such as Parkinson's disease (Hannay, et al. 2004).

In predisposed individuals risk factors induce the complex events that contribute to the development of dementia. It is possible that a brain injury causes a reduction of the cognitive reserve, and therefore cognitive decline affects functioning sooner than would have been the case if the injury had not happened; but dementia is a multi-factorial disease and a neuropathological hypothesis as to the relation between TBI and dementia are also present in literature (Shively et al., 2012).

A Clinical Neuropsychologist can provide an opinion on several issues that may be relevant to the topic discussed in this article such as: the severity of the brain injury, and if a brain injury is likely to have been sustained; the cognitive profile; the presence of any objective, vs. self-perceived, cognitive problems and their severity; the impact of cognitive impairment onto everyday life; and the risk of dementia following a TBI. ■

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References:

Ameducci L A, Fratiglioni, L, Walter A R, et al. (1986). Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. Neurology, 36: 922-931.

American Psychiatrist Association (APA, 2000). Diagnostic and Statistical Manual of Mental Disorders (4th edn) Text Revision (DSM-IV-TR). Arlington: APA.

Chen H, Richard M, Sandler D P, et al. (2007). Head injury and amyotrophic lateral sclerosis. Am J Epidemiol, 166:810-816.

Dams-O'Connor, K, Gibbons L E , Bowen J D, et al. (2012). Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. J Neurol Neurosurg Psychiatry. 84(2):177-82.

Fleminger S, Oliver D L, Lovestone S, et al. (2003). Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication J Neurol Neurosurg Psychiatry, 74:857.

Johnson V E, Stewart J E, Begbie F D, et al. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain, 136: 28-42.

Johnson V E & Stewart, W. (2015). Age at injury influences dementia risk after TBI. Nature reviews Neurology, 11: 128-130.

Johnson V E, Stewart J E, Begbie F D, et al. (2013). Inflammation and white matter degeneration persist for years after a single TBI. Brain, 136: 28-42.

Johnson V E, Stewart W, & Smith D H. (2012). Widespread τ and amyloid-β pathology many years after a single traumatic brain injury in humans. Brain pathology. 22(2):142-9.

Gardner R C & Yaffe K. (2015) epidemiology of mild traumatic brain injury and neurodegenerative disease. Molecular and cellular neurosciences, 6:75-80.

Gardner R C, Burke J, Nettiksimmons J, et al. (2014) Dementia risk after TBI vs. nonbrain trauma. JAMA Neurol, 71:1490-1497.

Gardner R C, Burke J F, Nettiksimmons J, et al. (2015). Traumatic brain injury in later life increases risk for Parkinson disease. Ann Neurol. 77(6):987-95.

Gavett B E, Stern R A, Cantu R C, et al. (2010). Mild traumatic brain injury: a risk factor for neurodegeneration. Alzheimer's Res Ther, 2:18.

Gavett B E, Stern R A, McKee A C. (2011). Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. Clin. Sports Med. 30(1): 179-188.

Godbolt A K, Cancelliere C, Hincapié C A, et al. (2014). Systematic review of the risk of dementia and chronic cognitive impairment after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil. 95(3): 245-56.

Goldman SM, Tanner CM, Oakes D, et al. (2006). Head injury and Parkinson's disease risk in twins. Ann Neurol, 60:65-72.

Guo Z, Cupples L A, Kurz A, et al. (2000). Head injury and the risk of AD in the MIRAGE study. Am Accad Neurology, 1316-1323.

Hannay, J., Howieson, D., Loring, D., Fischer, J. & Lezak, M. (2004). Neuropathology for Neuropsychologists, In M.D. Lezak, D.B. Howieson & D.W. Loring (Eds). Neuropsychological Assessment (4th Edition, pp. 157–285). Oxford: Oxford University Press.

Jordan B D, et al. (2000). Chronic traumatic brain injury associated with boxing. Semin Neurol, 20(2): 179-185.

Kay T, Harrington D E, Adams R et al. (1993). Definition of mild traumatic brain injury. J Head Trauma Rehab. 8(3): 86-87.

Lindsay J, Laurin D, Verreault R, et al. (2002). Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. 156: 445-453.

Launer L J, Andersen K, Dewey M E, et al. (1999). Rates and risk factors for dementia and Alzheimer's disease, results from EURODEM pooled analyses. Neurology, 78-84.

Lowenstein D H (2009). Epilepsy after head injury: an overview. Epilepsia. 50 Suppl 2:4-9.

Lye T C & Shores E A (2000). Traumatic brain injury as a risk factor for Alzheimer's disease: a review. Neuropsychol Rev. 10(2):115-29.

Mayeux R, Ottman R, Maestre G, et al. (1995). Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology. 45: 555-557.

McKee A C, Cantu R C, Nowinski CJ, Hedley-Whyte E T, et al. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropath, 68: 709-735.

McKee A C, Stein R A, Nowinski C J, et al. (2012). The spectrum of disease in chronic traumatic encephalopathy. Brain. 136(Pt 1):43-64.

Mehta K M, Ott M D, Kalmijn M D, et al. (1999). Head trauma and risk of dementia and Alzheimer's disease, The Rotterdam study. Neurology, 53: 1959-1962.

Mortimer J A, van Duijn C M, Chandra V, et al. (1991). Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol. 1991;20 Suppl 2:S28-35.

Nemetz P, Leibson C, Naessens J M, et al. (1999). Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. American Journal of Epidemiology, 149: 32-40.

Plassman B L, Havlik R J, Steffens D C, et al. (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 24: 55(8):1158-66.

Qiu C (2012). Preventing Alzheimer's disease by targeting vascular risk factors: hope and gap. J Alzheimer's Dis. 32 (3): 721-731.

Roberts G W, Whitwell H L, Acland P R, et al. (1990). The Lancet, 335: 918-919.

Saatman, K.E., Duhaime, A.C., Bullock, R., Maas, A.I., Valadka, A., Manley, G.T. et al. (2008). Classification of traumatic brain injury for targeted therapies, Journal of Neurotrauma, 25, 719–738.

Shively S, Scher A I, Perl D P, et al. (2012). Dementia resulting from traumatic brain injury: what is the pathology? Arch Neurol. 69(10):1245-51.

Smith D H, Johnson V E & Stewart W. (2013). Chronic neuropathologies of single and repetitive TBI: substrates of dementia? Nature reviews Neurology, 9:211-221.

Stein S C (1996). Classification of head injury. In Narayan R K, Povishock J T, Wilberg J E Jr (Eds). Neurotrauma. New York: McGraw-Hill (31-42).

Thornhill, S., Teasdale, G., Murray, G., McEwen, J., Roy, C. & Penny, K. (2000). Disability in young people and adults

one year after head injury: prospective cohort study. British Medical Journal, 320, 1631–1635.

Tyas S L, Manfreda J, Strain L A, et al. (2001). Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol. 30(3):590-7.

Vincent A S, Roebuck-Spencer T M & Cernich A (2014) Cognitive changes and dementia risk after traumatic brain injury: implications for aging military personnel. Alzheimers Dement. 10(3):174-87.

Williams D B, Annegers J F, Kokmen E, et al. (1991). Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. Neurology. 41(10):1554-7.

World Health Organization (2001). International Classification of functioning, disability and health. Geneva, Switzerland: WHO ■