Risk of Dementia Following Traumatic Brain Injury: A Review of the Literature
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Dementia

What is dementia?

Dementia is a general term for a decline in mental ability that interferes with daily life.

- It is not a disease
- It is a general term describing a group of symptoms

Major neurocognitive disorder DSM-5 Criteria

- Evidence of cognitive decline in one or more of the following:
  - Complex attention
  - Executive Function
  - Learning and Memory
  - Language
  - Perceptual-motor function
  - Social cognition

Alzheimer’s Disease (AD)

A diagnosis for individuals who have experienced cognitive decline related to onset and progression of Alzheimer’s Dementia (a neurological disorder related to the inclusion of beta amyloid plaques and neurofibrillary tangles in cholinergic neurons).

DSM-5 Diagnostic Criteria

A. Diagnostic criteria for major or minor neurocognitive disorder
B. Insidious onset and gradual decline of cognitive function in one or more areas
C. Diagnostic criteria for Alzheimer’s dementia are fulfilled by:
   (1) Presence of genetic mutation based on family history or genetic testing
   (2) Steady cognitive decline without periods of stability
   (3) No indicators of other physical, neurological, or medical problems responsible for cognitive decline

Media Presence

Brain Injury May Increase Risk of Alzheimer’s Disease
People who have a history of traumatic brain injury (TBI) may be at risk for developing dementia or Alzheimer’s disease earlier than those who didn’t have a TBI.

Contact sports associated with Lewy body disease, Parkinson’s disease symptoms, dementia

Alzheimer’s Disease (AD) found in 99% of studied brains from deceased NFL players

Media Presence

Study: CTE, other brain diseases can start earlier if tackle football player before age 12
By Danielle Burse, CNN
- Updated 2:29 PM ET, Mon July 24, 2017
Clinical Presentation of AD

Prevalence rate = 6-10% of 70yo+ *
Symptoms are progressive
Impair daily functioning
More severe than what is expected by normal age-related decline
- Forgetting recently learned information
- Asking the same questions again and again
- Difficulty creating and following a plan
- Trouble managing money
- Difficulty completing familiar tasks in familiar settings
- Confusion- losing track of date or where they are
- Difficulty with conversation - word finding or calling things the wrong name.
- Withdrawal from work/social activities
- Change in mood - confused, suspicious, depressed, fearful

* Prince et al., 2013, Brokmeier et al., 2011

Dementia with Lewy Bodies (DLB)

Diagnostic Criteria:
Meet Neurocognitive D/O criteria from DSM-V
Plus two of the following core symptoms:
- Fluctuating and unpredictable alertness and cognitive function
- Repeated visual hallucinations
- Parkinsonian symptoms
- REM sleep behavior disorder (act out their dreams during sleep)

Symptoms of DLB

Prevalence
<1 to 3 per 100,000 *
4.2% of all dementia cases in the community **
Common symptoms include:
- Cognitive problems (similar to Alzheimer's disease)
- Visual hallucinations
- Movement disorders
- Poor regulation of body functions (blood pressure, pulse, sweating, dizziness, falls, bowel issues)
- Sleep difficulties
- Fluctuating attention
- Depression
- Loss of motivation

* Zaccai et al., 2005
** Jones & O'Brien, 2014

Symptoms of FTLD

Pathological studies show compromise to the frontal and temporal regions of the brain, in contrast to global atrophy in AD

Diagnostic Criteria *
- Progressive decline in behavior or cognition
  - Disinhibition
  - Apathy
  - Emotionality
  - Executive functions (decision making, idea generation) with spared memory
- Age of onset often younger than other dementias

* Rascovsky et al., 2011

Frontotemporal Dementia (FTD)

FTD is a group of conditions in which nerve cell damage leads to loss of function in these brain regions, which variably cause deterioration in behavior and personality, language disturbances, or alterations in muscle or motor function.

Prevalence ranges from 2-20 per 100,000 (15 is thought to be best estimate) *
10-20% of all dementia cases
Three Variants
1. Behavioral variant - changes in personality and interpersonal relations
2. Primary Progressive Aphasia - language skills
3. Motor variant - changes in muscle or motor function without language or behavior problems

* Onyike & Diehl-Schmied, 2013; Knoppman & Roberts 2011

Table 1: Review of common causes of dementia, prevalence rates, typical age of onset, and symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic Criteria</th>
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<tr>
<td>Alzheimer's Disease</td>
<td>Progressive decline in behavior or cognition, disorientation, apathy, depression, difficulty with conversation, loss of motivation, hallucinations, delusions, etc.</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies (DLB)</td>
<td>Fluctuating and unpredictable alertness and cognitive function, repeated visual hallucinations, parkinsonian symptoms, REM sleep behavior disorder</td>
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<tr>
<td>Frontotemporal Dementia (FTD)</td>
<td>Progressive decline in behavior or cognition, disinhibition, apathy, emotional lability, executive dysfunction, young age at onset</td>
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Table Note: The table provides an overview of common causes of dementia, including prevalence rates, typical age of onset, and symptoms.
What is CTE?

Chronic Traumatic Encephalopathy
- A neurodegenerative disease
- Has been linked to repetitive head trauma
- Characterized postmortem by deposits of hyperphosphorylated tau in cells around blood vessels
- Dementia pugilistica (1928)
- Neuropsychiatric symptoms may accompany CTE but no clinical criteria established, unlike other dementias
  - Persistence of cognitive, behavioral, mood disturbances following head trauma

Limitations of CTE research

1. The majority of CTE researchers have examined donated brains from subjects who have already exhibited abnormal symptoms (e.g., NFL players who have committed suicide).
2. Many studies have not accounted for drug abuse, particularly opiate abuse, which is associated with CTE pathology (e.g., hyperphosphorylated tau) in up to 44% of brains (Solomon et al., 2014).
3. CTE is a rare condition, with less than 300 confirmed cases.
4. No prospective longitudinal studies of confirmed CTE to date.
5. Of note, only a handful of females (N=18) have ever been confirmed to have CTE.

TBI

TBI Severity

Glasgow Coma Scale, Loss of Consciousness, Imaging Findings, and Post-Traumatic Amnesia

Recovery after Moderate–Severe TBI

Clinical consensus is that cognitive recovery following TBI improves rapidly within the first 6 months after injury (Christensen et al., 2008).

Recovery curves are not uniform by domain (Hong et al., 2007) and are moderated by several factors:
- Age at injury is associated with cognitive improvement at 1-year post moderate to severe injury (Green et al., 2008). Those who have a younger age of injury have better cognitive improvement.
- Severity measures, such as LOC, PTA, and GCS can all influence cognitive recovery (Chu et al., 2007 & Spilker et al., 1999).
- Challenges: Attrition in longitudinal studies, practice effects, high variability among samples, and high variability among injury characteristics.

Long–term outcomes of TBI

What do we know about long-term (i.e., ≥ 5 years post-injury) recovery?
E.g., A 26-year-old male sustains a moderate–severe TBI, and at 1-year post-injury he returns back to work and living independently. He has mild to moderate cognitive impairments on several measures of neuropsychological testing but is using compensatory strategies to improve his daily functioning……

What can we say about his outcome ≥ 5 years from now?
### Long-term recovery after TBI

#### Cognitive Recovery
- Limited objective testing data more than 5 years post-injury
- Ruttan et al., 2008: Meta-analysis revealed that cognitive impairments persist > 4.5 years after injury
- Brown et al., 2011: Cognitive and emotional complaints are more likely to be reported than physical complaints decades after injury. Moderate-severe TBI survivors were significantly more likely to report memory, emotional, and physical problems.

#### Functional Recovery
- Brown et al., 2011: Majority of responders function at a high level without need for assistance. No injury-severity differences in educational or vocational attainment, marital status, income, personal relations, or quality of life were found. Time since injury was positively correlated with chances of complaints.

### Dementia Risk following TBI

#### 9 studies finding an association between TBI and dementia
- Geddes et al., 1999; Mayeux et al., 1999; O’Meara et al., 1997; Schrotz et al., 1997; Nomeziz et al., 1996; Gurevich et al., 2000; Plaisier et al., 2000; Ludlow et al., 2005; Banister et al., 2000; Brabant et al., 2000; Bowers et al., 2010; Law et al., 2013; Barnes et al., 2014; Gardner et al., 2014; Gilbert et al., 2014; Hinderstrom et al., 2014; Mendez et al., 2015; Liu et al., 2016; Deutrich et al., 2016; Peavy et al., 2016; Ludlow et al., 2016; Ludlow et al., 2017; Lubin et al., 2017; Li et al., 2017; Naj et al., 2017; Weiser et al., 2017; Ludlow et al., 2018; Schaffer et al., 2018; Hinderstrom et al., 2018; Gardner et al., 2018; Barnes et al., 2018

#### 9 studies not finding an association between TBI and dementia
- Fratiglioni et al., 1990; Law et al., 1999; Meltzer et al., 1996; Lindsay et al., 2002; Rapoport et al., 2008; Helmes et al., 2011; Dart-O’Connor et al., 2013; Xu et al., 2015; Craie et al., 2015; Cation et al., 2016

### Centers for Disease Control & Prevention:

“A TBI can also cause epilepsy and increase the risk for conditions such as Alzheimer’s disease, Parkinson’s disease, and other brain disorders.”

https://www.cdc.gov/traumaticbraininjury/outcomes.html

### Alzheimer’s Association:

“Over the past 30 years, research has linked moderate and severe traumatic brain injury to a greater risk of developing Alzheimer’s disease or another type of dementia years after the original head injury.”

“Not everyone who experiences a head injury develops dementia. There’s no evidence that a single mild traumatic brain injury increases dementia risk. More research is needed to confirm the possible link between brain injury and dementia and to understand why moderate, severe and repeated mild traumatic brain injuries may increase risk.”

https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/traumatic-brain-injury

### Institute of Medicine Committee:

“there is sufficient evidence of an association between moderate and severe TBI and dementia... limited/suggestive evidence of an association between mild TBI (with loss of consciousness) and dementia... and inadequate/insufficient evidence to determine whether an association exists between mild TBI (without loss of consciousness) and dementia.” (p214).

Moderating/Mediating Factors

Factors that influence dementia risk: Age at injury

Factors in those ≥ 65 years old were associated with increased dementia risk.

Older age at injury is associated with greater dementia risk.

Factors that influence dementia risk: Severity

More severe injuries are associated with higher dementia risk.

Factors that influence dementia risk: Frequency

Does repetitive TBI increase dementia risk more than a single moderate-severe TBI?

In Gardner et al., 2014, more than 1 TBI doubled the risk of dementia (56% increase) compared to a single TBI (26% increase) although they did not comment on severity of the injuries.

A more recent meta-analysis revealed no increased risk of neurologic or psychiatric disorder following multiple vs. single TBI (Perry et al., 2016). Chronic and repetitive TBI may be more associated with certain neurodegenerative conditions, such as CTE (Smith et al., 2013) versus AD, although this difference has not been thoroughly researched.

Factors that influence dementia risk: APOE ε4 alleles

Findings suggesting genetics moderates TBI and dementia risk are mixed. The protein apolipoprotein with the allele ε4 (APOE ε4) is one of the most established risk factors for AD.

APOE ε4 interacts with 

Mayeux et al., 1993 found the interaction APOE ε4 and TBI had this risk compared to APOE ε4 and TBI.

Isoniemi et al., 2006 – some individuals with APOE ε4 may have some long-term negative outcomes.

LoBue et al., 2017 observed no interaction between APOE ε4, TBI, and Age of Onset.

Factors that influence dementia risk: Severity

Table 2. Association Between TBI and Risk of Dementia Stratified by Age and TBI Severity

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<th>Age Group</th>
<th>HR (95% CI)</th>
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<td>Mild TBI</td>
<td>65-69</td>
<td>1.21 (1.01-1.44)</td>
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What does the research suggest?

1) Moderate to severe TBI likely increases risk.
2) Older age of injury may increase dementia risk.
3) More severe injuries increase dementia risk.
4) There may be genetic factors at play, but findings are mixed regarding APOE e4 alleles.
5) Dementia risk following repetitive injuries requires further investigation.

How does TBI increase dementia risk?

Mechanisms of TBI increasing dementia risk

Recall that dementias have multiple causes with different underlying neuropathology:
- AD (amyloid-beta + hyperphosphorylated tau)
- DLB (alpha-synuclein)
- FTLD (hyperphosphorylated tau or TDP-43)
- CTE (hyperphosphorylated tau or TDP-43)
- Vascular (white matter lesions or infarcts)
- PD (alpha-synuclein)

Dementia risk after TBI has varied between disease, suggesting that TBI may have different effects across neurodegenerative conditions.

The consensus is that TBI is likely a risk factor for AD in some individuals, perhaps interacting with tau or amyloid-beta. The risk is not as established in other neuropathologies.

The risk of TBI appears to be stronger for FTLD and AD, leading to earlier onset of symptoms in some individuals, possibly from increased neurodegenerative burden.

The association between TBI and LBD is less established.

Axonal injury is a hallmark pathology of TBI.

Axonal disruption can lead to intracellular beta-amyloid accumulation.

After cell-death, beta-amyloid is released into surrounding tissue, where it could form the beta-amyloid plaques seen in Alzheimer’s disease.
Multifactorial model:
Tau and beta-amyloid accumulation following TBI may interact with cerebrovascular and genetic factors.

Cognitive reserve:
Higher cognitive abilities at baseline may result in later onset or lower risk of dementia.

Neuronal reserve:
Higher brain volumes or greater resistance to neuropathology may delay onset or reduce risk of dementia.

TBI may simply result in a static, one-time lowering of cognitive or neuronal reserve, thus hastening age of onset and increasing risk of developing dementia.

If static effects are the only mechanisms...
Wouldn’t we expect the same dementia risk across all conditions?

| ANCOVA Results and Effect Size (adjusted for group sample size): |
|----------------------|---|---|---|---|---|---|---|
| TBI                |  N | M (SD) | M (SD) | M-diff | F (p-value) | d   |
| AD                 |  86 |  68.98 (10.2) |  66.16 (10.4) |  2.82 |  4.1 (0.043) |  0.78 |
| AD+LBD             |  137 |  67.82 (9.2) |  63.08 (9.8) |  4.74 |  6.8 (0.009) |  0.55 |
| LBD                |  320 |  69.94 (8.4) |  71.25 (11.2) |  1.31 |  0.59 (0.556) | -0.15 |
| FTLD               |  298 |  63.11 (9.4) |  59.01 (7.3) |  4.05 |  4.6 (0.031) |  0.54 |

Limitations of the literature
TBI has not been well characterized. Most studies rely on self-report of TBI. Variability exists among dementia criteria and TBI criteria. Vast majority of studies rely on clinical diagnoses of dementia, and accuracy of these diagnoses can vary depending on the neurodegenerative condition.

Age of dementia onset in autopsy-confirmed conditions. Schaffert et al., 2018 (in preparation), unpublished data.
Future directions in research

1. Determining mechanisms of how TBI may increase dementia risk in some individuals.

2. Longitudinal, prospective studies are needed. Several are currently underway (e.g., Professional Fighters Brain Health Study).

   Studies that well-characterize injury related factors along with dementia symptoms and disease course are needed.

3. Although media exposure is beneficial in terms of promoting brain health, objectivity continues to be needed within this field of research.

   E.g., Most individuals who sustain a TBI do not develop CTE or dementia.

Questions?

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References available upon request.