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Epidemiology of mild traumatic brain injury and neurodegenerative disease

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Abstract

Every year an estimated 42 million people worldwide suffer a mild traumatic brain injury (MTBI) or concussion. More severe traumatic brain injury (TBI) is a well-established risk factor for a variety of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Recently, large epidemiological studies have additionally identified MTBI as a risk factor for dementia. The role of MTBI in risk of PD or ALS is less well established. Repetitive MTBI and repetitive sub-concussive head trauma has been linked to increased risk for a variety of neurodegenerative diseases including chronic traumatic encephalopathy (CTE). CTE is a unique neurodegenerative tauopathy first described in boxers but more recently described in a variety of contact sport athletes, military veterans, and civilians exposed to repetitive MTBI. Studies of repetitive MTBI and CTE have been limited by referral bias, lack of consensus clinical criteria for CTE, challenges of quantifying MTBI exposure, and potential for confounding. The prevalence of CTE is unknown and the amount of MTBI or sub-concussive trauma exposure necessary to produce CTE is unclear. This review will summarize the current literature regarding the epidemiology of MTBI, post-TBI dementia and Parkinson's disease, and CTE while highlighting methodological challenges and critical future directions of research in this field.

Keywords

Chronic traumatic encephalopathy; Traumatic brain injury; Mild traumatic brain injury; Concussion; Neurodegenerative disease; Epidemiology

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Introduction

There is mounting epidemiological evidence that moderate or severe traumatic brain injury (TBI) is an important risk factor for neurodegenerative diseases such as Alzheimer's disease (AD)[1, 2] and Parkinson's disease (PD).[3] Relatively fewer studies have assessed the association specifically between mild TBI (MTBI) and neurodegenerative diseases, and thus this association is not as well established.[4, 5] Since the highly publicized report of a series of autopsy cases of professional American football players with chronic traumatic encephalopathy (CTE),[6, 7] however, there has been a resurgence of interest in unraveling the potential link between MTBI and neurodegenerative disease including CTE. This resurgence of interest has led to a number of recent studies that have investigated the risk of neurodegenerative diseases following MTBI or prevalence of neurodegenerative diagnoses or suggestive symptoms among individuals with high levels of exposure to repetitive MTBI. While this burgeoning field is rapidly making important new discoveries that are largely in support of a link between MTBI – particularly repetitive MTBI – and neurodegeneration, many questions remain. What is the population prevalence of CTE? What is the long-term risk of playing contact sports? What is the long-term risk of combat deployment and blast injury? How many head traumas (concussive or otherwise) are necessary to produce CTE? What are the biological mechanisms or risk factors?

Currently, CTE is a neuropathological diagnosis that cannot be made during life. Thus, all modern studies of CTE have been based on autopsy series while most large epidemiological studies of post-TBI neurodegenerative diseases have been based on clinical diagnoses of common neurodegenerative syndromes. Thus, the relationship between CTE neuropathology and post-TBI neurodegenerative syndromes (AD, PD, frontotemporal dementia, ALS) is unknown. It is plausible, for example, that some cases of clinically-diagnosed post-TBI AD, PD, or ALS actually reflect CTE neuropathology (or vice versa, as a significant minority of cases of CTE have had additional co-occurring neuropathologies[8]). This review will summarize the current literature regarding the epidemiology of MTBI, the epidemiology of post-TBI dementias and Parkinson's disease, and the epidemiology of CTE. Where appropriate, important avenues for future research will be highlighted.

What is MTBI?

The terms MTBI and concussion are often used interchangeably. Some would argue that these terms represent fundamentally different concepts and that concussion is a type of MTBI.[9] Sub-concussive injury refers to a traumatic impact to the head that does not result in any immediately appreciable clinical symptoms.[10] According to the World Health Organization Collaborating Center Task Force and the Centers for Disease Control and Prevention (CDC):

> "MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (1) one or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; and (2) Glasgow Coma Scale score of 13-15 after 30

> minutes post-injury or later upon presentation for healthcare. (3) These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury."[11]

The CDC has proposed specific International Classification of Diseases 9 (ICD-9) codes for the classification of MTBI.[12] These definitions are not yet universally used. A recent study[4] by the International Collaboration on Mild Traumatic Brain Injury systematically reviewed the MTBI diagnostic criteria used by the "best-evidence literature" pertaining to MTBI from 2001 through 2012. Among the 101 studies included in this review, there were more than 50 different MTBI definitions used. In light of this lack of consensus, workshops coordinated by the National Institute of Neurological Disorders and Stroke (NINDS), Department of Defense (DOD), and the National Institute on Disability and Rehabilitation Research (NIDRR) have establishment a multidisciplinary effort to develop TBI Common Data Elements (TBI-CDEs),[13] which were first published in 2010 and then revised in 2012. Thus, all data presented in the remainder of this review must be interpreted in this context.

How common is MTBI and repetitive MTBI?

MTBI is extremely common. It is estimated that 100 to 300 per 100,000 people seek medical attention for MTBI annually worldwide.[14] Because many people with MTBI may not seek medical attention,[15] it is likely that the true global population incidence of MTBI exceeds 600 per 100,000 people annually (or roughly 42 million people worldwide every year), with most cases being due to falls or motor vehicle collisions.[14] The prevalence of repetitive MTBI is less clear. It is known that prior TBI is a risk factor for future TBI,[16] though risk specifically pertaining to MTBI is not known.

Certain sub-populations such as contact sport athletes (including American football, boxing, ice hockey, mixed martial arts, and soccer), military personnel, and victims of domestic violence are at particularly high risk for suffering MTBI, repetitive MTBI, and repetitive sub-concussive head trauma. Interestingly, TBI exposure across many of these high-risk populations has not remained stable over time – a phenomenon known to epidemiologists as a "secular trend." For example, a study of professional boxers in the United Kingdom and Australia found that from 1930 to 2003 the average professional boxer's career duration dropped nearly 75% (from 19 to 5 years) while the average number of career bouts dropped 96% (from 336 to 13).[17] This reduction in exposure over time paralleled increases in medical oversight and raises the possibility that the quality of chronic neurologic sequelae of boxing may change over time as well.[18] Similarly, professional American football has changed dramatically over the past few decades, with increasing medical oversight and changes to protective gear and rules of play aimed specifically at improving player safety. It is possible, however, that increased body padding and improved helmets could, paradoxically, increase the frequency and severity of traumatic hits sustained by players due to an increased sense of personal safety (i.e. "risk compensation").[19] Modern tracking devices have found that players currently sustain thousands of sub-concussive hits to the head during a single season.[20, 21] Lastly, among military veterans, mortality following TBI

has declined dramatically since the Vietnam war, leaving an increasing number of military veterans living with sequelae of TBI and potentially being at heightened risk of repeat TBI. War tactics have also changed such that blast injuries, which frequently result in mild-TBI (or sub-concussive head trauma), are extremely common. A recent survey of deployed troops in Operation Iraqi Freedom and Operation Enduring Freedom found that 17% reported MTBI during deployment, and of these, 59% reported more than one MTBI.[22] Thus, some secular trends may be associated with reduced exposure to repetitive MTBI while other secular trends may be associated with heightened exposure.

Apart from secular trends, there may be cohort effects between different sports and different types of military-related MTBI.[23] That is, the biomechanics and resultant neuronal injury of an MTBI sustained by a football player may differ from those incurred by a boxer or blast-exposed military veteran. Along these lines, early reports of CTE in boxers more frequently reported parkinsonism as a presenting symptom[24] compared to modern series of CTE comprised mainly of non-boxers.[25]

These estimated statistics, secular trends, and cohort effects highlight the critical importance of ongoing research to better characterize and quantify MTBI exposure, particularly among specific high-risk populations.

Does TBI increase risk for neurodegeneration?

Many studies have assessed risk of common neurodegenerative diseases following TBI. Meta-analyses of many of these prior studies have shown a significantly increased risk associated with history of TBI for the development of AD,[1, 2] PD,[3] and ALS.[26] Two studies have additionally identified TBI as a risk factor for frontotemporal dementia.[27, 28] Thus, while there is solid epidemiological evidence in support of TBI as a risk factor for many neurodegenerative diseases, additional research is needed to answer a number of outstanding questions. For example, since many prior studies have been based on retrospective determination of TBI, large well-powered prospective confirmatory studies are needed. Creative population-based approaches need to be developed to capture cases of TBI that may not present to medical attention and may differ systematically from those who do.[15] The selection of controls requires careful consideration in order to reduce the likelihood of confounding or reverse-causation[29] (e.g. if a patient suffers a TBI due to incipient neurodegenerative disease or if patients prone to TBI differ systematically from those not prone to TBI). Lastly, a few exciting studies have found that specific genes or other exposures may independently or synergistically increase risk for neurodegeneration after TBI[30, 31, 32] (see risk factors, below), highlighting the need for further studies of risk modifiers or mediators of post-TBI neurodegenerative diseases.

Does MTBI increase risk for neurodegeneration?

The majority of prior epidemiological studies assessing risk of neurodegenerative diseases following TBI have focused either on risk imparted by a TBI of any severity or of risk imparted by a moderate or severe TBI. For example, two systematic reviews of risk of dementia following MTBI[33, 34] that jointly covered the world literature from 1980 through 2012 identified only four qualifying studies.[35-38] Of these four studies, two reported a

significant association between MTBI and dementia.[36, 37] All four, however, were limited by a relatively small number of MTBI-exposed patients. Since 2012, several larger studies employing national registries of administrative health data have specifically assessed risk of dementia followed single MTBI. One study of one million adult Taiwanese patients, reported that MTBI was associated with a greater than 3-fold increased risk of dementia.[39] The average time from MTBI to dementia diagnosis in this study was one year, raising the possibility of reverse-causation. A subsequent study of over 800,000 male military conscriptees followed for over 30 years, reported a 70% increased risk of young onset non-AD type dementia (before age 65) after MTBI.[40] The authors, however, speculated that this small magnitude of risk was likely due to residual confounders that were not accounted for in the study. Lastly, in our own analysis of over 160,000 trauma patients aged 55 and older in which we compared risk of dementia following MTBI versus limb fracture (in order to mitigate potential reverse-causation or confounding), we found that MTBI was significantly associated with a 22-26% increased risk of dementia over the subsequent 5 to 7 years, but only among patients aged 65 and older at the time of TBI.[41] Taken together, these studies suggest that there is likely a small, but significant, risk of dementia following a single MTBI that is not solely due to reverse-causation or confounding. It is likely, however, that younger adults may be more resilient or may take longer to develop dementia than older adults who sustain a MTBI.

Risk of PD following MTBI is less clear. A systematic review of the literature from 1990-2012 identified just five high-quality studies assessing risk of PD after MTBI.[5] Of the two studies that reported an elevated risk of PD after MTBI, the study authors themselves were not convinced, attributing their positive results to reverse-causation in one study[29] and sub-optimal matching of controls in the other.[42] The other three studies in the meta-analysis, however, did not find an association between MTBI and PD.[43-45] Additional well-powered studies of risk of PD following MTBI that carefully consider reverse-causation and matching of controls are warranted.

Does repetitive MTBI increase risk for neurodegeneration?

Risk of neurodegenerative diseases following *repetitive* MTBI or repetitive sub-concussive head injuries has recently been assessed most thoroughly among contact sport athletes such as professional American football players. A study of death certificates among retired NFL players found a three-fold elevated rate of dying from neurodegenerative causes compared to the typical population frequency, particularly for AD and ALS.[46] On the other hand, a study of aging adults who played high school American football in Rochester, Minnesota between 1946 and 1956 found no increased rate of later developing dementia, PD, or ALS.[47] It is unclear to what degree this study may apply to modern day high school athletes given the changes in the sport over the past half century.

The epidemiology of chronic traumatic encephalopathy is largely unknown

CTE is a neurodegenerative tauopathy linked to exposure to repetitive MTBI. CTE has been associated with mood, behavior, cognitive, and/or motor symptoms (including parkinsonism and/or motor neuron disease)[25, 48] that may closely resemble AD, PD, frontotemporal

dementia, or even ALS. Recently reported cases have typically developed progressive neurobehavioral symptoms years or decades following exposure to MTBI,[25] although at least one incipient case of CTE has been reported in a high-school football player who died unexpectedly.[49] Because CTE is a neuropathological diagnosis, the prevalence of CTE in the general population is unknown. To date, large population-based studies of CTE have not been possible due to the lack of consensus clinical diagnostic criteria for CTE, thus precluding diagnosis during life. Estimates of prevalence of CTE must then rely upon autopsy series of neuropathologically confirmed cases of CTE or clinical case series assessing prevalence of suggestive clinical syndromes in populations exposed to repetitive MTBI such as professional contact sport athletes or military veterans. Furthermore, among epidemiological studies reporting an association between TBI (or MTBI or repetitive MTBI) and neurodegenerative syndromes that lack autopsy-confirmation, the degree to which these clinical syndromic diagnoses reflect true PD, AD, frontotemporal dementia, ALS, CTE, or any combination of the above, remains unknown. Table 1 outlines just a few of the methodological challenges facing epidemiological studies of CTE. Table 2 provides definitions of pertinent epidemiological terminology.

An association between repetitive MTBI and chronic or progressive neurologic dysfunction was first reported in the medical literature by Harrison S. Martland in his 1928 report, “Punch Drunk.”[50] The report consists of one detailed case description of a professional boxer who retired at the age of 23, after 7 years in the ring, due to left hand tremor and gait unsteadiness. Despite retirement, this patient's symptoms progressed. By age 38, his symptoms were indistinguishable from PD. Although Martland does not report any specific data in this regard, and had personally examined only five symptomatic boxers, he stated that “almost 50 percent of fighters” develop progressive impairments that usually begin with slightly “flopping” of one foot or leg while walking or slight gait unsteadiness which may then be followed by periods of slight mental confusion as well as bradykinesia and may, in the most severe cases, progress to severe parkinsonism and mental deterioration.

Subsequent to this report, others began publishing similar case reports or small case series of neurologic sequelae of boxing.[51-53] The syndrome became known as dementia pugilistica[52] as it was believed to occur primarily in boxers. On review of some of these early cases, it seems likely that at least some cases reflected chronic neurologic deficits due to acute brain contusions or hemorrhages sustained during a boxing bout rather than progressive neurodegenerative disorders. In the absence of medical oversight of boxing at that time, high-resolution neuroimaging studies, or detailed neuropathological descriptions of dementia pugilistica, however, a determination of underlying etiology in these early cases was not possible. It was not until the 1960s and 70s that autopsy reports of a unique degenerative neuropathology, eventually termed CTE, was correlated with the syndrome of dementia pugilistica.[24, 54]

In 1969, Roberts published a highly cited clinical study of 250 randomly sampled boxers from a cohort of over 16,000 boxers registered in the UK between 1929 and 1955 that reported that 17% of sampled boxers showed neurologic deficits attributable to boxing.[55] While this early clinical study remains the best attempt to assess an unbiased population prevalence of boxing-associated neurologic sequelae, it is unclear what proportion of these

cases may have had neuropathological evidence of CTE.[56] Lastly, given dramatic changes in rules of play, medical oversight, and duration and intensity of boxing careers since these early studies were performed, extrapolation of this result to modern day boxers or other athletes, military personnel, or civilians exposed to repeated MTBI is challenging.

Since the first recognition of CTE in a professional American football player in 2005,[6] a number of subsequent modern cases and case-series of CTE have been reported. The largest modern autopsy series to date, that included 85 patients exposed to repetitive MTBI (including 64 athletes and 21 military veterans), identified evidence of CTE in 68 patients (80%).[8] Today, American football remains the sport most commonly associated with autopsy-proven CTE in the modern medical literature. Recent autopsy series assessing rates of CTE among former professional American football players have reported prevalence ranging from 50% to 97%,[8, 49, 57] though all of these reports are limited by referral bias. Interestingly, however, one of these studies that included 35 former professional American football players[8] found that the neuropathological stage of CTE significantly correlated with number of years of football exposure, lending weight to a true causal association.

Consensus clinical criteria for CTE[58, 59] are needed in order to facilitate population-based epidemiological studies of CTE incidence and prevalence.[54, 55] The overlap between CTE-associated symptoms and other common neurodegenerative syndromes suggests that consensus research criteria will likely require a combination of TBI exposure history, clinical features, and neuroimaging[60] or body fluid biomarkers.[61] Thus, ongoing efforts to identify potentially unique clinical features of CTE and to develop and refine biomarkers of CTE are critically important. Lastly, prospective, longitudinal studies of high-risk subgroups are needed to better quantify MTBI exposure, subsequent risk of CTE, and additional risk factors for CTE, as are already underway among boxers[62] and recently returned U.S. military veterans.[63]

Risk Factors for Post-TBI Neurodegenerative Diseases and CTE

The absence of CTE neuropathology in some multiply-concussed professional American football players[57] as well as the absence of neurodegenerative disease in the majority of adults with a history of prior MTBI or concussion, suggests that there must be multiple additional risk and protective factors that determine whether an individual person develops a post-TBI neurodegenerative disease.

Apolipoprotein E (APOE) ε4 allele, the strongest susceptibility gene for AD, is associated with modified risk for many neurodegenerative diseases following TBI.[48, 64-67] This association between APOE allele and CTE, however, remains unclear given competing results of recent studies.[54, 62, 64] Specific mutations in genes encoding α-synuclein have been associated with increased risk of PD after TBI[30, 31] and this risk is augmented in a more than additive manner with exposure to paraquat-containing pesticides[32] (Table 3).

It is unknown whether recreational drug or steroid use, alcohol abuse, chronic psychiatric disease, or cardiovascular risk factors modify risk of CTE, though these conditions may have been over-represented in modern autopsy series of CTE comprised largely of professional athletes. There is some evidence that TBI in children or adolescents may be

particularly morbid.[71, 72] On the other hand, we have found that older adults are at higher risk of dementia after MTBI compared to middle-aged adults.[41] These results suggest that there may be “critical periods” during which TBI may be more likely to produce chronic neurologic sequelae or neurodegeneration. Gender effects are also understudied. The vast majority of cases of CTE have been in males, presumably due to referral bias.

Summary

MTBI is extremely common affecting roughly 42 million people annually worldwide. Definitions of MTBI across studies are inconsistent, highlighting the need for ongoing efforts to develop and refine TBI common data elements. Moderate or severe TBI is an established risk factor for neurodegenerative diseases such as dementia, PD, and ALS. Recently, large epidemiological studies have reported that MTBI and repetitive MTBI are also significant risk factors for neurodegenerative diseases, but these associations are not yet as well established and require further replication. CTE is a neuropathological diagnosis that has been associated with repetitive MTBI exposure. Prevalence of CTE is unknown due to referral bias limiting autopsy studies and lack of consensus clinical criteria limiting unbiased population-based studies. Among athletes exposed to extremely high levels of repetitive MTBI or repetitive sub-concussive head traumas, such as former American football players, CTE has been reported in 50% to 97% of players that have gone to autopsy. Consensus clinical diagnostic criteria for CTE are needed. Clinical overlap between symptoms associated with CTE and other more common neurodegenerative diseases such as AD and PD suggest that CTE clinical criteria will likely require a combination of TBI history, clinical symptoms, and biomarkers. Improved quantification of MTBI exposure as well as prospective longitudinal studies of outcomes and risk factors will be critical to elucidate the actual burden of neurodegenerative diseases including CTE among athletes, military personnel, and civilians exposed to single or repetitive MTBI.

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Abbreviations

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
CTE	chronic traumatic encephalopathy
MTBI	mild traumatic brain injury
PD	Parkinson's disease
TBI	traumatic brain injury

Highlights

- Mild traumatic brain injury (MTBI) is extremely common.
- Some studies have found an association between MTBI and neurodegenerative diseases.
- Chronic traumatic encephalopathy (CTE) is associated with repetitive MTBI.
- Prevalence of CTE is unknown as it can only be diagnosed on autopsy.
- Large prospective longitudinal studies of MTBI and neurodegeneration are needed.

Table 1
Methodological Challenges of Epidemiological Studies of CTE

Challenge	Consequence
Lack of consensus clinical criteria for CTE.	Prevalence/incidence can only be inferred from autopsy series, which are often limited by referral bias.
Variable definitions for MTBI used in prior studies.	Hinders comparison across studies.
Objective quantification/measurement of repetitive MTBI exposure is difficult.	Population studied may have very heterogeneous MTBI exposures. Amount of MTBI exposure necessary to produce pathology is unknown.
Recall bias	Symptomatic patients may be more likely to report MTBI exposure or less likely to recall MTBI exposure (if memory is affected).
Selection or referral bias	Results are not broadly applicable to general population
Finding the appropriate control group is difficult.	Potential for confounding as MTBI-exposed populations may differ from healthy controls in many ways besides MTBI exposure.
Secular trends: frequency and quality of MTBI exposure has changed dramatically among athletes and military personnel over the past century	Unclear to what degree older studies may be applied to modern patients
Cohort effects: MTBI sustained in American football may differ considerably from MTBI sustained in boxing or combat.	Unclear to what degree studies of one cohort of patients exposed to repetitive MTBI may be applied to other cohorts.
CTE symptoms may not appear until years or decades following MTBI exposure	Prospective studies from time of exposure to symptom onset may take decades to yield results. Retrospective studies may be influenced by recall bias or poorly quantified exposure.

Abbreviations: CTE = chronic traumatic encephalopathy; MTBI = mild traumatic brain injury

Table 2
Definitions of Pertinent Epidemiological Concepts

Epidemiological Term	Definition
Selection/Referral Bias	This is a source of systematic error in which study participation is not random and therefore is not representative of the entire population of interest. This may confound and/or limit generalizability of the results.
Recall/reporting bias	This is a type of systematic error in which the accuracy of reporting of prior events systematically differs between study participants (e.g. between cases and controls). This may be of particular concern in retrospective studies based on chart review but may also effect any study measurement that relies upon self or informant report.
Confounding	The observed association between a predictor and an outcome is not due to a causal relationship. Rather, the association is due to a third factor, which influences both the predictor and outcome. This concern can be mitigated by adjusting analyses for confounders or matching cases and controls based on confounders.
Reverse-causation	The outcome is the cause of the predictor. Thus, while the predictor and outcome will be associated, the causal arrow is in the reverse direction from what is expected/hypothesized.
Secular trend	Changes in characteristics of a disease over time, which may be due to changing external factors.
Cohort effect	Unique characteristics of a disease in a specific cohort due to a shared exposure, year of birth, or other shared life experience.

Table 3
Possible Risk Factors for Post-TBI Dementia, PD, and CTE

Risk Factor Category	Dementia	PD	CTE
Demographic	Increasing age[40, 41]	Increasing age[68]	Increasing age[8]
Genetic	APOE allele[64]	Alpha-synuclein genotype[30, 31]	Competing results for APOE allele[8, 48, 67]
TBI factors	>1 TBI[41]	>1 TBI[45, 68]	Repetitive MTBI[8, 49, 69]
	More severe TBI[40, 41]	More severe TBI[3, 5]	Repetitive sub-concussive head trauma[70]
	Exposure to contact sports[46]	Exposure to contact sports[52,46]	Exposure[69] and duration of exposure[55] to contact sports
Other environmental exposures		Paraquat exposure[32]	

Abbreviations: APOE = apolipoprotein; TBI = traumatic brain injury. Other abbreviations per Table 1.