Clinical Phenotype of Dementia after Traumatic Brain Injury

Nasreen Sayed,¹ Carlee Culver,² Kristen Dams-O'Connor,³ Flora Hammond,⁴ and Ramon Diaz-Arrastia^{1,2}

Abstract

Traumatic brain injury (TBI) in early to mid-life is associated with an increased risk of dementia in late life. It is unclear whether TBI results in acceleration of Alzheimer's disease (AD)-like pathology or has features of another dementing condition, such as chronic traumatic encephalopathy, which is associated with more-prominent mood, behavior, and motor disturbances than AD. Data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set was obtained over a 5-year period. Categorical data were analyzed using Fisher's exact test. Continuous parametric data were analyzed using the Student's *t*-test. Nonparametric data were analyzed using Mann-Whitney's test. Overall, 877 individuals with dementia who had sustained TBI were identified in the NACC database. Only TBI with chronic deficit or dysfunction was associated with increased risk of dementia. Patients with dementia after TBI ($n=62$) were significantly more likely to experience depression, anxiety, irritability, and motor disorders than patients with probable AD. Autopsy data were available for 20 of the 62 TBI patients. Of the patients with TBI, 62% met National Institute of Aging-Reagan Institute "high likelihood" criteria for AD. We conclude that TBI with chronic deficit or dysfunction is associated with an increased odds ratio for dementia. Clinically, patients with dementia associated with TBI were more likely to have symptoms of depression, agitation, irritability, and motor dysfunction than patients with probable AD. These findings suggest that dementia in individuals with a history of TBI may be distinct from AD.

Key words: Alzheimer's disease; chronic traumatic encephalopathy; National Alzheimer's Coordinating Center

Introduction

TRAUMATIC BRAIN INJURY (TBI) is a major public health problem in modern societies, primarily a consequence of traffic accidents and falls. In the United States alone, an estimated 1.7 million people sustain a TBI annually, of which 275,000 require hospitalization and 52,000 die.¹ In developing countries, rates are even higher.² TBI is the leading cause of death and disability for persons between the ages of 1 and 44 years, and an estimated 5.3 million Americans, almost 2% of the population, live with long-term disabilities resulting from a previous TBI.³ The segment of the population with the highest rates of TBI hospitalizations and deaths are the elderly. In the elderly, falls are the primary cause of TBI hospitalizations and deaths, whereas traffic accidents are the primary cause in adolescents and young adults.¹

TBI is perhaps the best-established environmental risk factor for dementia.⁴ A meta-analysis of 15 case-control studies⁵ concluded that a history of head injury of sufficient severity to result in loss of consciousness was associated with an increased risk of dementia. These case-control studies suffer from potential recall bias, an inherent limitation of the retrospective design, but one prospective

study on this issue provides convincing data on the association between TBI in early to mid-life and late-life dementia. Plassman and colleagues⁶ studied U.S. Navy and Marine veterans who were hospitalized for TBI in the Pacific theater during World War II, who were compared to veterans hospitalized for non-TBI injuries at the same time. When followed over 50 years after the injury, severe TBI (sTBI; defined as loss of consciousness or post-traumatic amnesia lasting longer than 24 h) was associated with a hazard ratio (HR) for dementia of 4.41 [95% confidence interval (CI), 2.09–9.63]. Moderate TBI (defined as loss of consciousness or post-traumatic amnesia lasting longer than 30 min, but less than 24 h) yielded an HR of 2.39 (95% CI, 1.24–4.58). In this study, there was no increased risk of dementia in veterans who suffered a mild TBI (mTBI; loss of consciousness or post-traumatic amnesia less than 30 min). On the basis of these and other studies, an Institute of Medicine committee recently concluded that "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."⁷

¹Department of Neurology, University of Texas Southwestern Medical Center, Dallas, Texas.

²Center for Neuroscience and Regenerative Medicine, Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

³Department of Rehabilitation Medicine, Mt. Sinai School of Medicine, New York, New York.

⁴Department of Physical Medicine and Rehabilitation, Indiana University School of Medicine, Indianapolis, Indiana.

Although the long-term consequences of single episodes of primarily moderate-to-severe TBI have only recently been recognized, it has long been known that multiple mTBIs result in late-life dementia. This was initially recognized in professional boxers⁸ and, more recently, has been described in former professional football and hockey players.^{9,10} This syndrome, termed chronic traumatic encephalopathy (CTE), is distinct from Alzheimer's disease (AD) clinically and pathologically. Clinically, CTE is characterized by prominent problems with mood, behavior, irritability, and motor symptoms, whereas memory problems, though present, are less prominent at onset.^{8,10,11} Pathologically, CTE is characterized by the prominence of tau-reactive neurofibrillary tangles in the superficial cortical layers, frontal and temporal cortices, and sulcal depths, with few or no amyloid plaques.^{9,10} Although CTE was initially described in 1928,⁸ its true prevalence is unknown, because consensus clinicopathological criteria do not exist. Earlier studies on the association in the general population have not analyzed the prevalence of affective, behavioral, or motor symptoms in patients with dementia after TBI. There is also a paucity of pathologic data on patients who have died with TBI-associated dementia.

It is unclear whether brain trauma in early to mid-life in life leads to an acceleration and higher risk of AD-type pathology or whether TBI-associated dementia is a distinct pathologic entity, such as CTE. Understanding the features of dementia associated with TBI is critically important to society. Though, currently, there are no effective therapies available to treat or prevent AD, several such therapies are on the horizon.¹² Studies in aging populations have been successful in identifying imaging and biochemical biomarkers of the early stages of AD,¹³ information that is critical to the development and application of effective therapies. If TBI victims are at increased risk of AD-type neurodegeneration, early recognition is essential to implement preventive therapies. Alternatively, if TBI survivors experience dementia as a result of an alternate pathologic process, such as CTE, identifying early and pre-clinical diagnostic biomarkers is an essential first step for developing effective therapies.

The National Alzheimer's Coordinating Center (NACC) maintains a database of clinical and pathologic information collected by National Institute on Aging (NIA)-funded Alzheimer's Disease Centers (ADCs). Since September 2005, all ADCs have collected data using a Uniform Data Set (UDS), allowing pooling of data across different centers. UDS data are collected prospectively by clinicians, neuropsychologists, and other ADC research personnel, using up to 18 standardized forms at each visit.¹⁴ Neuropathology data are also collected using uniform data fields, completed by a neuropathologist at each center.¹⁵ The UDS includes three questions regarding previous exposure to TBI.

In this study, we queried the NACC UDS database to determine whether patients with dementia who reported having experienced a TBI demonstrate clinical or pathological features distinct from patients with a diagnosis of probable AD who had not suffered a TBI. First, we hypothesized that previous TBI exposure was associated with increased odds of dementia. Second, we hypothesized that patients with dementia reporting a TBI have features atypical for AD, but consistent with CTE. Specifically, we hypothesized that compared with patients with probable AD, patients with dementia and a TBI history would have (1) younger age of onset, (2) increased prevalence of mood and behavior symptoms early in the course, and (3) for those that have come to autopsy, the predominant pathology will be a tau-only dementia, with relatively modest plaque pathology.

Methods

The NACC UDS database was queried encompassing patients evaluated at ADCs from September 2005 through December, 2010. The NACC is the depository for prospectively collected data from all 29 ADCs throughout the United States. These participating sites conduct clinical and biomedical research in demented and non-demented patients using case-report forms that record clinical symptoms and signs elicited during memory clinic visits, a focused neuropsychologic battery, as well as neuropathological information for patients who expire. Full details regarding UDS data have been published¹⁴ and are available on the Web (www.alz.washington.edu). The UDS is divided into Initial Visit Packet (IVP), Final Visit Packet, Telephone Follow-up, and a Milestone Form. The IVP is comprised of 18 standardized forms, which cover the sociodemographics on subject and informant, family history, dementia history, neurological exam findings, functional status, neuropsychological test results, clinical diagnosis, whether imaging testing was completed, and apolipoprotein E (ApoE) genotype. The Neuropathology Data Set (NP) encompasses demographics, date of death, primary and secondary neuropathological diagnoses, presence or absence of neuropathological features of most major dementias, ApoE genotype, and brain weights. Information was obtained from the IVP (included in the UDS) and, when available, the NP. Data collected through the NACC were approved by institutional review boards at each participating ADC.

Clinical information at the initial visit to participating ADCs was obtained through structured interviews. For this study, the focus was on three questions included in the UDS Subject Health History Form (Form A5, Question 4), which related to previous TBI and gauged the intensity of injury. All UDS subjects (demented or controls) were asked whether they (1) had experienced a TBI resulting in a brief (<5-min) loss of consciousness (LOC), (2) had experienced a TBI resulting in extended LOC (≥ 5 min), or (3) had experienced a TBI resulting in chronic deficit or dysfunction. Each question could be answered as absent, recent/active, remote/inactive, or unknown. Recent/active was defined as if it happened within the last year or still required active management and was consistent with information obtained from informant report, medical records, and/or observation. Remote/inactive was coded when the TBI occurred in the past (greater than 1 year ago), but was resolved or there was no current treatment underway.

The NACC database also includes the consensus clinical diagnosis for each patient, according to established criteria.¹⁴ Clinicians at each ADC were asked to provide a primary clinical diagnosis of one of the following: probable AD; possible AD [both based on National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria]; dementia with Lewy bodies; vascular dementia; frontotemporal lobar degeneration; or other miscellaneous conditions, including TBI. Clinicians were also asked to code possible contributing secondary diagnoses. A clinical diagnosis of probable AD means that in the opinion of a consensus committee of experts in dementia, AD is most likely the pathologic diagnosis. A clinical diagnosis of possible AD means that in the opinion of the consensus committee, AD is the most likely pathologic diagnosis, but that atypical features of other confounding comorbidities may be contributing to the clinical picture. The clinical course of patients with a possible AD diagnosis is very similar to those with a probable AD diagnosis, and these two diagnostic classifications are often lumped together in the AD field.¹⁶ Full details of the criteria used in the NACC clinical diagnosis are available in the NACC Coding Guidebook (available at: www.alz.washington.edu).

Because the initial query found an association between dementia and TBI only for those subjects who had experienced a TBI resulting in chronic deficit or dysfunction, further analysis focused on this group. Cases were subjects with dementia who had experienced a TBI resulting in chronic deficit or dysfunction. Control subjects (2 controls for each case) were a random sample of patients with a NINDS-ADRDA¹⁷ diagnosis of probable AD who answered no to all three TBI questions and were matched for gender and education with the cases.

Statistical analysis

The odds ratio (OR) for dementia between the brief LOC, extended LOC, and chronic deficit or dysfunction were assessed using Fisher's exact test. Cases (subjects with dementia who reported a TBI with chronic deficit or dysfunction, $n=62$) were compared to controls who had a diagnosis with probable AD and no history of TBI ($n=122$) using Fisher's exact test for categorical assessments (behavioral assessments, clinical judgment of symptoms, and other neurological conditions) or Mann-Whitney's test for ordinal and nonparametric variables [Hackinski Ischemic Score, Unified Parkinson's Disease Rating Scale, Geriatric Depression Scale, and Mini-Mental State Examination (MMSE)]. Detailed descriptions of each instrument and their psychometric properties have been published.¹⁴ For cases and controls with autopsy data, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuritic Plaque Score, Braak and Braak stage, Amyloid Angiopathy Score, and Diffuse Lewy Body Rating was analyzed using the chi-square test. All statistical analyses were done using GraphPad Prism v. 4.0 for Windows (GraphPad Software, San Diego, CA). A false discovery rate ≤ 0.05 was used to correct for multiple comparisons.

Results

The NACC database contained 8381 patients with dementia and 7862 healthy controls. Approximately 10% of individuals with dementia ($n=878$) reported having sustained TBI. Of these, 567 had brief LOC, 248 had extended LOC, and 62 had chronic deficit or dysfunction. TBI with chronic deficit or dysfunction was associated with a significantly increased risk for dementia (Table 1). There was no increased risk of dementia for TBI associated with extended LOC or with brief LOC. The consensus clinical diagnosis for these 62 individuals with dementia who had suffered a TBI with chronic deficit or dysfunction was probable AD 25 (40%), possible AD 9 (14%), brain injury 5 (8%), Lewy body dementia 3 (5%), vascular disease 1 (2%), and undetermined 19 (30%).

The 62 patients with dementia who suffered TBI with chronic deficit or dysfunction were compared to a gender- and education-matched group of 122 patients with probable AD who did not report a TBI (Table 2). Only parameters that were significantly different

(uncorrected $p < 0.05$) between cases and controls are included in Table 2. TBI patients were significantly more likely to experience depression, anxiety, irritability, and motor disorders. Memory complaints were less common at the initial visit among individuals with TBI, but there was no difference in the MMSE. Comparing only the 34 patients who indicated that their TBI was remote/inactive to the controls, similar ORs were found for each of the symptoms or signs.

Autopsy data were available for 20 of the 62 TBI patients and for 16 of the 122 non-TBI controls (Table 3). Of the patients with TBI, 62% met NIA-Reagan high likelihood criteria, and 69% met CERAD criteria for definite AD. There was no difference in the Braak and Braak stage between cases and controls. However, cases had significantly lower CERAD Neuritic Plaque Score and Amyloid Angiopathy Score.

Discussion

In this study using NACC UDS data, a self-reported history of TBI with chronic deficit or dysfunction is associated with an increased OR for dementia. Unlike other studies,^{5,18} we did not find that "TBI resulting in loss of consciousness" was associated with an increased OR for dementia. A key feature of our study was the use of three questions to characterize TBI severity and duration of associated deficits, whereas most earlier studies relied on a single question, resulting in the lumping of more-severe TBIs in with milder injuries. Our results were more consistent with the one study on this issue that did not rely on retrospective ascertainment of TBI severity,⁶ which did not find that mTBI (LOC less than 30 min) resulted in higher risk of dementia. They are also consistent with the majority of studies on this issue, which were recently reviewed by the Institute of Medicine,⁷ which did not find convincing evidence of an association between single episodes of mTBI and dementia. These findings should provide some comfort from a public health perspective, because mTBI is a very common experience in modern life. However, because the NACC UDS data are not based on an epidemiologically designed population-based sample, these results are not definitive, and carefully conducted prospective studies are needed.

We were also not able to find support for our hypothesis that TBI resulted in an earlier age of onset of dementia, compared to probable AD. Existing pathology-based series¹⁰ of CTE resulting from participation in contact sports indicate that age of onset is typically in the fifth or sixth decades of life, substantially younger than the typical age of onset of AD. Although comforting, the findings of this study must be considered tentative until epidemiologically sound studies are completed. Age of onset is a difficult phenotype to assess, particularly using retrospective ascertainment, as is the case in the NACC UDS. Future studies using prospective ascertainment of incident dementia will be needed to assess this important issue. Also, our study did not look at rate of progression of dementia symptoms. Such data were prospectively collected in the NACC UDS and is the focus of a future study.

The major contribution of this work is that unlike databases used in earlier studies, the NACC UDS database has extensive data on the clinical features and neurobehavioral signs and symptoms, allowing a more comprehensive characterization of dementia phenotype as expressed in individuals with and without a history of TBI. Compared to patients with typical probable AD who had never sustained a TBI, patients with dementia who had sustained a TBI with chronic deficit or dysfunction were more likely to have symptoms of depression, agitation, irritability, and motor

TABLE 1. ODDS RATIO OF DEMENTIA AFTER TBI

	OR	95% CI	p value
TBI with brief LOC	0.998	0.883–1.113	0.9960
TBI with extended LOC	1.078	0.896–1.298	0.4520
TBI with chronic deficit or dysfunction	3.060	1.828–5.121	<0.0001

TBI, traumatic brain injury; OR, odds ratio; CI, confidence interval; LOC, loss of consciousness.

TABLE 2. DEMOGRAPHIC AND BEHAVIORAL SYMPTOMS COMPARING CASES AND CONTROLS

<i>Demographic</i>	<i>TBI with chronic deficit or dysfunction (n = 62) (Mean ± SD)</i>	<i>No TBI probable AD (n = 122) (Mean ± SD)</i>	<i>p value (uncorrected)</i>	<i>Significant FDR < 0.05</i>
Age at onset of dementia (years)	66.9 ± 12.5	64.4 ± 11.0	ns	
Age at initial evaluation (years)	72.4 ± 12.1	70.2 ± 10.8	ns	
Education (years)	14.1 ± 3.1	14.5 ± 4.0	ns	
Gender (% male)	65.1	64.5	ns	
Ethnicity (% Caucasian)	82.5	87.9	ns	
	<i>OR</i>	<i>95% CI</i>	<i>p value</i>	
<i>Behavioral assessment</i>				
Agitation	2.073	1.095–3.925	0.033	*
Depression	2.229	1.185–4.194	0.016	*
Irritability	1.934	1.032–3.627	0.041	
Nighttime behaviors	2.400	1.263–4.449	0.009	*
<i>Clinical judgment of symptoms</i>				
Memory	0.051	0.003–0.933	0.0070	*
Fluctuating cognition	11.52	0.556–238.5	0.0660	
Depression	2.038	1.185–4.194	0.0160	*
Psychosis	2.038	1.162–3.574	0.0150	*
Disinhibition	2.637	1.150–6.048	0.0310	*
Irritability	2.106	1.096–4.049	0.0310	*
Agitation	2.100	0.967–4.560	0.0700	
Personality Change	3.505	1.624–7.566	0.0020	*
Gait Disorder	4.594	2.198–9.600	<0.0001	*
Falls	6.886	2.694–17.60	<0.0001	*
Tremors	2.909	1.247–6.787	0.0160	*
Slowness	3.962	1.988–7.899	0.0001	*
<i>Other neurological conditions</i>				
Seizures	45.19	2.58–791.6	<0.0001	*
<i>Ordinal measures</i>	<i>Median</i>	<i>Median</i>	<i>p value</i>	
MMSE	22	21	0.475	
GDS	2	1	0.088	
UPDRS	12	2	<0.0001	*
Hachinski Ischemic Score	1	0	<0.0001	*

TBI, traumatic brain injury; AD, Alzheimer's disease; FDR, false discovery rate; SD, standard deviation; ns, not significant; OR, odds ratio; CI, confidence interval; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 3. PATHOLOGIC FINDINGS COMPARING THE TBI WITH CHRONIC DEFICIT OR DYSFUNCTION AND NO TBI GROUP

<i>Ordinal measures</i>	<i>Chi-square</i>	<i>df</i>	<i>p value</i>
CERAD Neuritic Plaque Score	8.99	3	0.029
Braak and Braak stage	2.85	6	0.826
NIA-Reagan likelihood of dementia resulting from AD	3.85	2	0.146
DLB clinical syndrome resulting from DLB pathology	3.14	2	0.209
<i>Dichotomized measures</i>	<i>OR</i>	<i>95% CI</i>	<i>p value</i>
Amyloid angiopathy dichotomized	0.13	0.026–0.674	0.026
Braak and Braak dichotomized	0.73	0.591–3.380	1.000

TBI, traumatic brain injury; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NIA, National Institute on Aging; AD, Alzheimer's disease; DLB, diffuse Lewy body; OR, odds ratio; CI, confidence interval.

dysfunction. These findings are consistent with our hypothesis that individuals with a history of TBI who become demented demonstrate clinical features that are distinct from AD and consistent with CTE. Although the majority of individuals with TBI were diagnosed with probable or possible AD during life, a substantial minority had an "undetermined" coding for clinical diagnosis in the UDS. In only 8% was brain injury recognized as being associated with dementia by ADC clinicians. This indicates that, in most cases, a neurodegenerative process beyond the recognized and stable sequelae of TBI dominated the clinical picture. It also reflects the protean and varied features of dementia experienced by older adults with a history of TBI, as well as the difficulty faced by experienced clinicians in making the diagnosis in the absence of established diagnostic criteria or discriminating imaging and biochemical biomarkers.

Pathologically, the majority of TBI patients met CERAD criteria for definite AD or NIA-Reagan high likelihood that dementia was the result of AD. However, when the CERAD Neuritic Plaque Score and Amyloid Angiopathy Score were analyzed, patients with

dementia with a history of significant TBI had lower amyloid burden than those with typical AD. There was no difference in the Braak and Braak stage, suggesting comparable degrees of tau pathology in patients with dementia who had been exposed to a TBI, compared to those with probable AD. These findings are consistent with our hypothesis, because CTE is predominantly a tauopathy and differs from AD because of a relative paucity of amyloid pathology.

CTE was not diagnosed pathologically in any of the cases who came to autopsy in this study. CTE is not a specific diagnosis code in the NACC Neuropathology data forms, which focus on the pathological features of AD, diffuse Lewy body disease, frontotemporal lobar degeneration, and vascular pathology. Despite having been described over 40 years ago,¹¹ CTE is considered a curiosity by most neuropathologists and is believed to occur only in retired professional athletes. Progress in the field will require validated criteria for the pathological diagnosis of CTE, which remain to be developed.

Our study suffers from several limitations that warrant consideration. Most important, the ascertainment of TBI relies on self-report by the participant or caregiver, and recall bias is an inherent limitation of retrospective data collection. This problem is somewhat ameliorated by the fact that only TBI with chronic deficit or dysfunction was considered, because recall bias is less likely concerning an injury that resulted in a chronic disability. Another major limitation is that data were not collected in the UDS regarding how long before the onset of dementia the TBI occurred. If the time from injury to onset of dementia is short, the concern that the TBI was a consequence of the preclinical stages of the neurodegenerative disease, or that symptoms represent enduring effects of a recent TBI, cannot be ruled out. We believe these explanations are unlikely, because there was no difference in the results when patients whose TBI was rated as remote/inactive were analyzed separately. The UDS has no information on the number of TBI exposures. CTE is described in individuals who suffer multiple TBIs, and it is unknown whether a single moderate or severe TBI results in CTE-like pathology. Further, no information was available regarding the type of chronic deficit or dysfunction resulting from TBI. Finally, readers are cautioned to keep in mind that the injury severity classification in this study, as defined by the three TBI exposure questions, does not map onto currently used terminology of mild, moderate, and severe TBI. There is a paucity of validation of the three TBI-related questions in the NACC database, which are not widely used in the brain-injury research field. It is well recognized that some individuals with mTBI may have chronic deficit or dysfunction. There is a great need for prospective clinicopathological studies of TBI survivors.

We conclude that the clinical and pathologic phenotype of dementia-associated TBI may be distinguishable, in part, from AD and may share some features with CTE. However, we did not find an earlier age of onset for dementia associated with TBI. These findings have implications for the development of therapies aimed to prevent dementia in individuals who sustain a TBI and will require confirmation in careful prospective clinicopathological studies.

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Author Disclosure Statement

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Address correspondence to:
Ramon Diaz-Arrastia, MD, PhD
Center for Neuroscience and Regenerative Medicine
Uniformed Services University of the Health Sciences
12725 Twinbrook Parkway
Rockville, MD 20852

E-mail: Ramon.Diaz-Arrastia@usuhs.mil