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An exploration of clinical dementia phenotypes among individuals with and without traumatic brain injury

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Abstract

OBJECTIVE—To characterize the clinical profiles of individuals with dementia who do and do not report a history of TBI.

INTRODUCTION—Some evidence suggests that a history of traumatic brain injury (TBI) is associated with an increased risk of dementia later in life. The clinical features of dementia associated with TBI have not been well investigated. While there is some evidence that TBI is associated with increased risk of Alzheimer's disease (AD), there are also indications that dementia associated with TBI has prominent behavioral, affective, and motor symptoms, making it distinct from AD.

METHODS—The current study involves secondary analysis of baseline data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS).

RESULTS—Individuals with dementia who reported a history of TBI had higher fluency and verbal memory scores and later onset of decline, but they are on more medications, had worse cardiovascular and cerebrovascular health, were more likely to have received medical attention for depression, and were more likely to have a gait disorder, falls, and motor slowness.

CONCLUSION—These findings suggest that dementia among individuals with a history of TBI may represent a unique clinical phenotype that is distinct from known dementia subtypes.

Keywords

Dementia; traumatic brain injury (TBI); National Alzheimer's Coordinating Center (NACC)

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Declaration of interest

None of the authors have any conflicts of interest to report.

1. Introduction

Traumatic brain injury (TBI) is a major public health problem in the United States, as approximately 10% of the population reports having sustained at least one lifetime TBI which led to a hospitalization (Corrigan, Whiteneck, & Mellick, 2004; Whiteneck et al., 2004), and an estimated 5.3 million Americans (approximately 2% of the population) live with long-term physical and psychological impairments that limit their independence and ability to work (Langlois, Rutland-Brown, & Wald, 2006; Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999).

As TBI survivors age, the risk of neurodegenerative disorders such as dementia and parkinsonism is a growing concern among patients, caregivers, and clinicians. Although the evidence is mixed, several studies have found an association between lifetime TBI and dementia risk in late life (Institute of Medicine Committee on Gulf War and Health, 2009). Elderly individuals experience a particularly high incidence of TBI, and some experience a rapid decline in neurologic function in the years following injury (e.g., (Mosenthal et al., 2002; Susman et al., 2002)). The pathologic features of post-TBI neurodegeneration are poorly understood. It is unclear whether the cognitive and functional decline experienced by some TBI survivors mimics AD or other known dementias, or represents a unique degenerative process related to the injury. Chronic traumatic encephalopathy (CTE) (McKee et al., 2009) is one example of a distinct pathological process found in postmortem brain tissue of some athletes exposed to multiple concussions and that may also occur after single TBI (Omalu, Hamilton, Kamboh, DeKosky, & Bailes, 2010). Retrospective reports suggest that CTE is characterized by depression, irritability, impulsivity, motor symptoms, and to a lesser extent by memory problems and executive dysfunction (Corsellis, Bruton, & Freeman-Browne, 1973; Gavett et al., 2011; Martland, 1928). Although no clinical diagnostic criteria for CTE exist at this time, the disease appears to share many symptoms with AD and other dementia syndromes, making it challenging to characterize and diagnose during life.

While the severity and duration of TBI-related symptoms can vary tremendously across individuals, many people who sustain more severe injuries experience lasting and even lifelong impairment. Cognitive changes after TBI often include deficits in attention, processing speed, and executive functioning (Gordon & Hibbard, 2005; Lezak, Howieson, & Loring, 2004) and emotional consequences include depression, anxiety, behavioral impulsivity and agitation/aggression (Ashman, Gordon, Cantor, & Hibbard, 2006; Hibbard, Rendon, Charatz, & Kothera, 2005; Hibbard, Uysal, Kepler, Bogdany, & Silver, 1998). Physical symptoms can include fatigue, headaches, balance problems, seizures, and endocrine dysfunction (Hibbard, Uysal, Sliwinski, & Gordon, 1998). Moreover, for some individuals, a TBI sustained earlier in life can result in worsening functional impairment later in life (Marquez de la Plata et al., 2008), when injury-related impairments interact with age-related decline. Not surprisingly, older adults with TBI perform more poorly on measures of attention and verbal memory compared to age-matched healthy controls (Ashman et al., 2008). Older adults with TBI report more metabolic and endocrine problems, in addition to more neurologic symptoms (i.e., headache, sensory changes), compared to age-matched healthy peers (Breed et al., 2008). Some metabolic symptoms, such as thyroid problems, are more common among older adults with TBI as compared to matched peers and younger adults with TBI, suggesting increased likelihood of medical comorbidities among individuals with TBI as they age (Breed, Flanagan, & Watson, 2004; Flanagan, Hibbard, & Gordon, 2005; Flanagan, Hibbard, Riordan, & Gordon, 2006).

Given that individuals with enduring TBI-related impairments may experience increased difficulty as they age such that their overall health and cognition are worse than age-

matched peers, it seems that there is a strong possibility of misdiagnosis in late life. Given the symptom overlap between TBI and known dementias, misdiagnosis in older adulthood may occur if TBI history is not fully considered.

After reviewing the literature on long-term consequences of TBI, the Institute of Medicine (IOM) recently concluded that moderate and severe TBI is associated with increased risk of dementia (Institute of Medicine Committee on Gulf War and Health, 2009). Several large-scale studies have not found an association between TBI and dementia (Dams-O'Connor et al., 2012; Mehta et al., 1999; Williams et al., 1991). Because it is not known whether a unique TBI-related dementia syndrome exists, it is possible that post-TBI cognitive and functional decline is misdiagnosed or misattributed to common dementing processes such as AD, thereby supporting a relationship between TBI and AD that may not accurately account for post-TBI decline. Identification of the clinical phenotypic features that distinguish between individuals with TBI, other neurodegenerative conditions, and normal aging is necessary to make accurate diagnoses and ultimately to develop preventive and therapeutic strategies.

TBI and dementia are heterogeneous clinical conditions that can unfold variably over time across individuals. There is a paucity of neuropathologic information regarding the cellular and histologic hallmarks of TBI in long-term survivors, and neuropathologic data has not been correlated with the phenotypic characteristics of the person across the longitudinal course of the disease. The etiology of cognitive and functional impairments among older adults who have a history of TBI is particularly nebulous, and presents an important barrier to treatment planning. Precise diagnosis of dementia subtypes based on their natural histories and clinical presentation is necessary for more accurate prognoses. A more comprehensive understanding of the clinical characteristics of dementia among individuals with a history of TBI can allow for an improved classification approach that can allow for appropriate alignment between treatment options and disease type as more interventions become available.

The ideal study in which to systematically evaluate post-TBI decline and compare its clinical characteristics to that of neuropathologically verified diagnoses of known dementias has not yet been conducted. Several high quality longitudinal studies of cognitive aging exist that utilize research quality consensus-based dementia diagnosis methods but do not adequately assess for TBI history or characterize the severity or sequelae of TBIs. The National Institute on Disability and Rehabilitation Research TBI Model Systems national database is the largest longitudinal prospective study of TBI outcomes in the United States and boasts excellent characterization of the injury and its acute course, but lacks cognitive assessment or dementia screening at follow-up. Despite known limitations, existing datasets can be used to begin to learn more about the clinical features that may distinguish individuals with TBI who are later diagnosed with dementia from individuals with dementia who have no TBI history.

The current study uses data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) to determine whether individuals with dementia who report a history of TBI demonstrate cognitive, health, or functional symptoms that are distinct from those seen in individuals with a diagnosis of dementia who did not report a history of TBI.

2. Methods

The NACC maintains a database of clinical information collected by 34 past and present National Institute of Aging (NIA) funded Alzheimer's Disease Centers (ADCs) throughout the United States. Since September 2005, all ADCs have collected data using a UDS that includes clinical symptoms and signs elicited during memory clinic visits, and a focused

neuropsychological battery, allowing data to be pooled from participating centers. UDS data are collected prospectively by clinicians, neuropsychologists, and other ADC research personnel (Morris et al., 2006). Data from the current study were gathered using the NACC Initial Visit Packet (IVP), which is comprised of 18 standardized forms that are used to record sociodemographic information about the subject and informant, family history, health history, neurological exam findings, functional status, neuropsychological test results, and clinical dementia diagnosis at the time of study entry. The current study includes data collected at ADCs between September 2005 and May 2012. Institutional Review Board approval was secured at each participating ADC for all data submitted to NACC.

2.1. Clinical evaluation

Clinical information at the initial visit to participating ADCs was obtained through structured interviews with the participant and his/her informant, neurological exam, medical record review, and neuropsychological evaluation (Morris et al., 2006; Weintraub et al., 2009). Demographic information included age, sex, race, and educational history. Information on previous history of TBI was gathered using three questions included in the UDS Subject Health History Form (Form A5, Question 4) that asked whether the subject: (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. Absent was coded if TBI history was not reported or indicated by information available from informant report, medical records, or observation. Recent/Active was coded if the TBI 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 if the TBI occurred in the past (greater than one year ago) but there was no current treatment underway. In the current study, we coded both recent/active and remote/inactive endorsements as positive for a previous history of TBI. In order to minimize retrospective recall bias, our analyses include only those individuals who reported a TBI with extended LOC or chronic deficit/dysfunction, as these more severe injuries are more likely to be accurately recalled.

2.1.1. Cognitive functioning—Information on participants' cognitive functioning was collected in the UDS using the following standardized tests:

Mini Mental State Examination **(MMSE; (Folstein, Robins, & Helzer, 1983)):** The MMSE is a 30-point screening assessment for cognitive impairment in areas of orientation, attention, concentration, memory, language, and visual construction.

Wechsler Memory Scale-Revised **(Wechsler, 1987b); select subtests:** Logical Memory I and II, Digit Span Forward, Digit Span Backward. The Logical Memory Test assesses immediate and 30-minute delayed recall of 25 units of information in a story that is read aloud. The Digit Span Forward test assesses immediate memory span for verbally presented numbers. Digit Span Backward is a measure of short-term concentration that requires examinees to repeat verbally presented numbers in reverse order.

Wechsler Adult Intelligence Scale-Revised **(Wechsler, 1987a); select subtests:** Digit Symbol. The Digit Symbol subtest engages multiple cognitive functions (e.g., attention, psychomotor speed, visual scanning) by requiring the participant pair symbols and numbers according to a key.

Category Fluency Test **(Butters, Granholm, Salmon, Grant, & Wolfe, 1987):** The Category Fluency Test assesses the ability to correctly generate examples from two categories (animals and vegetables) within two consecutive one-minute periods.

Trail Making Test **(Reitan & Wolfson, 1985):** The Trail Making Test consists of 2 parts. Trail Making A (Trails A) requires examinees to draw lines connecting circled numbers in consecutive order to measure visuomotor speed and tracking. Trail Making B (Trails B) requires an additional element of executive functioning by asking examinees to draw lines to connect letters and numbers in an alternating ascending sequence.

Boston Naming Test **(BNT; (Kaplan, Goodglass, & Weintraub, 1983)):** The BNT assesses confrontational naming through visual presentation of simple drawings. The UDS uses 30 drawings for a maximum score of 30 for the number of spontaneously correct (i.e., un-cued) responses.

2.1.2. Psychiatric functioning—Psychiatric functioning was assessed in the current study through clinical interview, medical record review, informant report, and participant self-report. Data were gathered using the UDS Subject Health History Form (Form A5) on episodes of depression requiring medical attention in the past two years or remote history of the same. Standardized assessments used to assess psychiatric functioning included the following:

Neuropsychiatric Inventory Questionnaire **(NPI-Q; (Kaufer et al., 2000)):** The NPI is administered to caregivers to assess multiple domains of psychopathology in dementia. The NPI-Q is brief version of the NPI that screens for presence and severity of symptoms in each domain.

Geriatric Depression Scale **(GDS; (Sheikh & Yesavage, Jun 1986)):** The GDS consists of 15 self-report yes-no questions inquiring about the participant's mood over the past week.

2.1.3. Medical history and health—The UDS Subject Health History Form (Form A5) was used to collect information on current and past medical conditions. Responses were coded as Absent, Active, or Inactive as described above, and in the current study both active and inactive reported conditions were coded as positive for that condition. A composite score of cardiovascular health is comprised of the following current and past conditions: heart attack/cardiac arrest, atrial fibrillation, angio-plasty/endarterectomy/stent, cardiac bypass procedure, pacemaker, and congestive heart failure. A composite of cerebrovascular conditions includes stroke and transient ischemic attack, and a composite of other medical or metabolic conditions includes hypertension, hyper-cholesteremia, diabetes, B12 deficiency, and thyroid disease. Total scores were calculated for each of these three health domains by summing positive responses. Data were also gathered on number of medications being taken at the time of the evaluation.

Substance abuse history was queried through a series of questions regarding clinically significant impairment over a 12-month period in the areas of work, driving, legal, or social functioning resulting from either alcohol use or other abused substances (e.g., recreational drugs). Cigarette smoking history was collected through a series of questions about smoking patterns within the past 30 days.

2.1.4. Clinical characterization of dementia—Participants at each ADC undergo a physical and neurological exam, which is coded in the UDS through a series of items, including age and pattern of onset of decline. An additional UDS form completed by the

examining clinician (B9; Clinician Judgment of Symptoms) is coded using information gained from the subject, informant, medical records, and clinical observations records information on three areas of functional decline: cognition (e.g., memory, judgment, language), behavior (e.g., apathy, depression, agitation), and motor symptoms (e.g., gait disorder, falls, tremor, motor slowness). Clinicians also used information from medical exams and medical records to calculate Hachinski Ischemic Score (HIS) which provides overall characterization of dementia symptoms. (Rosen, Terry, Fuld, Katzman, & Peck, 1980) Data on independent functioning is collected through informant interview using the *Functional Assessment Questionnaire* (*FAQ*; (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982)). The FAQ provides a structured interview to be administered to a caregiver to assess ability to perform ten complex activities of daily living. Activities that were not performed premorbidly are not scored, and the total score is pro-rated accordingly.

The NACC database also includes the consensus-based or clinician-rated clinical diagnosis for each participant seen at a participating ADC according to established criteria for probable AD or other dementia subtypes. Clinicians at each ADC were asked to provide a primary clinical diagnosis of a known dementing condition or subtype, such as: Probable AD, (based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria (McKhann, Drachman, & Folstein, 1984), Dementia with Lewy Bodies, Vascular Dementia, Alcohol-related dementia, Frontotemporal Lobar Degeneration, Primary Progressive Aphasia, or Corticobasal degeneration. Clinicians were also asked to code possible contributing diagnoses, such as TBI. Full details of the criteria used in the NACC clinical diagnosis are available in the NACC Coding Guidebook (available at www.alz.washington.edu).

2.2. Sample

Cases ($n = 332$) were subjects with dementia who had experienced a TBI resulting in extended LOC (>5 minutes) or a TBI resulting in chronic deficit or dysfunction. Control subjects (2 controls for each case; $n = 664$) were a random sample of patients with a diagnosis of dementia (of any type) who were coded as "Absent" for all three TBI questions. Cases and controls were matched by age (within 3 years) and education (within one year).

2.3. Data analysis

Statistical analyses focused on evaluating differences between cases (individuals with dementia and history of TBI) and controls (individuals with dementia and no history of TBI) in the areas of cognitive functioning, psychiatric functioning, medical history and health, clinical characteristics of dementia, and dementia diagnosis using data collected at the baseline (first) NACC study visit. First, descriptive information on age, gender, race and educational history were calculated to describe the sample. Prior to statistical analysis, cases were weighted 0.5: 1 with controls to avoid issues with unbalanced designs, which can often lead to homogeneity of variance problems. Then, differences between groups were evaluated using chi-square, Fisher's Z, *t*-tests, and Mann Whitney tests as appropriate. Effect sizes were calculated for comparisons of cognitive functioning indices. Hierarchical regressions were used to evaluate group differences in indices of cognitive functioning that differed between groups, controlling for age and sex. The level of significance was set as $p < 0.05$, and significance level was adjusted for false discovery rates by domain (cognitive functioning, psychiatric functioning, medical history and health, clinical characteristics of dementia, and dementia diagnosis) (Benjamini & Hochberg, 1995). Statistical analyses were conducted using SPSS 19.0 (SPSS, Inc., Chicago, USA).

3. Results

As of May 2012, the NACC database contained 332 demented individuals who reported a history of TBI with either extended LOC, chronic deficit/dysfunction, or both, at their initial visit. Of the 332 individuals reporting a history of TBI, there were 287 TBIs with extended LOC reported and 69 TBIs with chronic deficit/dysfunction reported, which means that 24 people reported one of each type of injury. Two matched control cases for each TBI case were randomly selected from the NACC database based on age (within 3 years) and education (within one year). Demographic data for each group are summarized in Table 1. There were no differences between groups in educational status, and both groups were over 80% Caucasian. Consistent with previous literature on TBI incidence (Faul M, Xu L, Wald MW, & Coronado VG, 2010), there were more males in the TBI group. Despite the attempt made to match cases on age, individuals with TBI are approximately three years older than controls ($p < 0.05$). Although three years was not deemed to represent a clinically significant difference for the purpose of the current study, we ran additional analyses of cognitive functioning indices (which may be somewhat sensitive to age effects) that controlled for age and sex. Cases were excluded from individual analyses if they were missing information on target variables, but were retained for all analyses of non-missing data (thus N's vary slightly for each of the analyses reported below).

A comparison of cognitive test results among cases and controls indicates that individuals with a history of TBI performed slightly better on measures of immediate memory (Logical Memory IA), delayed memory (Logical Memory IIA), and category fluency (Animals) (False discovery rate, $p \leq 0.012$); differences between groups in mental status (Mini Mental State Examination), and speed and accuracy of visual scanning and sequencing (Trails B time, Trails B total number of correct lines) did not remain significant after adjustment for multiple comparisons ((Benjamini & Hochberg, 1995); see Table 2). Effect sizes for these comparisons were small (0.07–0.15). Overall, even though the sample was not limited to individuals with specific dementia syndromes (e.g., Alzheimer's disease), there was very little variability in cognitive test scores. When cognitive test results were regressed on group (case or control) controlling for age and sex, differences in test performance by group remained only for immediate and delayed memory; however, very little variance was accounted for in these models. For the model predicting immediate memory performance, age and sex (entered in step 1) were not significant [$F(2, 540) = 2.92$; $R^2 = 0.011$; $p = 0.055$], but group (TBI or no TBI; entered in step 2) was [$F(3, 539) = 3.74$; $R^2 = 0.020$; $p = 0.011$]. For the model predicting delayed memory performance, age and sex (entered in Step 1) were both significant predictors [$F(2, 531) = 9.51$; $R^2 = 0.035$; $p = 0.000$], as was group (TBI or no TBI; entered in Step 2) [$F(3, 530) = 8.22$; $R^2 = 0.044$; $p = 0.000$].

The next set of analyses examined differences between cases and controls on clinical indices of psychiatric functioning. The groups did not differ in level of depression reported on the GDS, but there was a trend toward more frequent depressive disorders requiring medical attention among individuals with a history of TBI (see Table 3). Individuals with a history of TBI also had more psychiatric symptoms as reflected by higher scores on the NPI-Q ($p < 0.05$).

Comparisons between groups on indices of medical history and current health indicate poorer overall health among individuals with a history of TBI. Those with a history of TBI have higher sum scores for cardiovascular health and cerebrovascular health (indicating more health problems), but there were no differences between groups in current or past medical/metabolic conditions (see Table 4). Individuals with a history of TBI took a greater number of medications ($p < 0.021$). There were no significant differences in alcohol use, substance use, or cigarette smoking history across the groups (see Table 4).

The next set of analyses explored differences in clinical characterization of dementia symptoms among those with and without a history of TBI. Individuals with a history of TBI were judged to have a later age of onset of dementia [mean (SD) 67.03 (11.46) years] compared to those with no history of TBI [64.54 (10.55) years], t(df) =−2.86(634), p = 0.004. There were no differences between groups in clinicians' judgment of the presence of current cognitive impairments relative to previous abilities, including memory, judgment and problem solving, language, visuospatial functioning, or attention/concentration (p > 0.05). Similarly, there were no differences between groups in clinicians' judgment of the presence of current behavioral symptoms, including apathy/withdrawal, depression, auditory hallucinations, delusional beliefs, behavioral disinhibition, irritability, agitation, or personality change (p > 0.05); however, clinicians did find that 14% of individuals with a history of TBI experienced visual hallucinations as compared to 8.2% of those with no history of TBI (Pearson Chi-square = 6.04, p = 0.049). There were differences between the groups in clinicians' ratings in several categories of motor symptoms. Although there was no difference in the presence of clinically notable tremor across groups (p > 0.05), those with a history of TBI were more likely than those without a TBI to have a gait disorder characterized by shuffling walk, unsteadiness, limited arm swing, or dragging a foot that is not due to arthritis or injury (35.8% vs. 22.5%; Pearson Chi-square = 14.59, p = 0.001), a recent increase in falls (25.9% vs. 12.4%; Pearson Chi-square = 19.87, p < 0.000), and were somewhat more likely to have motor slowness (slowed walking or moving) (34.4% vs. 25.4%; Pearson Chi-square = 6.96, p = 0.031). Individuals with a history of TBI were judged to have higher clinician-rated Hachinski Ischemic Scores (mean (SD) 1.5 (2.12)) compared to those with no history of TBI (1.02 (1.50)), t(df) =−3.35(631), p = .001). There were no differences between groups in ability to perform activities of daily living as measured by the FAQ (p > 0.05).

The NACC contains a variety of empirically supported diagnostic classifications for dementia, and the final set of analyses compared the frequency of syndromic diagnosis across individuals with and without a history of TBI. Most notably, individuals with a history of TBI were significantly less likely to be diagnosed with Probable AD (45.1% of Dementia cases with TBI) than those with no TBI (55.9% of cases) according to NINCDC/ADRDA criteria (see Table 5). Diagnoses of other dementia syndromes were comparably rare, but results indicate that individuals with a history of TBI were slightly more likely than controls to be diagnosed with Vascular dementia or Corticobasal Degeneration (not statistically significant after correction for false discovery rate; see Table 5). Interestingly, of 321 cases included in these analyses who had a diagnosis of dementia and a history of TBI, TBI was judged by the clinician to be a "primary" cause of dementia in only 6 (1.9%) cases, and TBI was considered to be a "secondary" cause of dementia in only 36 (11.2%) cases.

4. Discussion

The current study used the UDS database to explore clinical characteristics of individuals with dementia who did and did not report a history of TBI with extended LOC or chronic deficit/dysfunction. Several discernible differences were found between individuals with and without a history of TBI, despite the fact that overall variability in functioning was limited in a sample of individuals with dementia. Not surprisingly, many differences reported here were subtle and effect sizes were small.

Results of the current study indicated that demented individuals with and without a history of TBI may present with clinical characteristics that differ in subtle but meaningful ways. Compared to individuals with dementia but no history of TBI, those with a history of TBI had better cognitive functioning in the areas of immediate and delayed memory and word fluency. However, those with a history of TBI had worse psychiatric functioning as

measured by the NPI-Q and slightly higher incidence of clinically significant depression. Those with TBI also had worse cardiovascular and cere-brovascular health, and were taking a greater number of prescription medications. In terms of clinical characterization of dementia symptom onset, those with and without TBI did not differ in clinician ratings of cognitive or behavioral symptom profile, but those with TBI were more likely to have visual hallucinations, a gait disorder, recent falls, and motor slowness.

The clinical profile of post-TBI dementia seen in the current study does overlap considerably with the symptom presentation reported in individuals who have been diagnosed with CTE posthumously; these features include mood and behavioral symptoms such as depression, irritability, and impulsivity; motor symptoms such as gait disturbance and slowing; and changes in memory and executive functioning (Corsellis et al., 1973; Gavett et al., 2011; Martland, 1928). The findings reported here also suggest that poor overall health and high medical comorbidity may be more common among demented individuals with a history of TBI, which is consistent with more recent conceptualizations of TBI as a chronic disease process with secondary medical conditions that may unfold over time (Masel & DeWitt, 2010).

Those with a history of TBI in the current study also had a later onset of dementia by an average of 3 years, and the TBI group was about 3 years older than those with no history of TBI. This is in contrast to findings from other studies, which have found an earlier onset of dementia among individuals with TBI (e.g., Mehta et al., 1999). It is possible that those with a history of TBI in the current study simply waited longer to seek medical evaluation for functional decline because they had other pressing problems (e.g., health concerns and mood disorders) or because dementia-like symptoms weren't immediately recognized as representing new problems for individuals with residual TBI-related impairments. Together, these differences in symptom presentation may have contributed to a greater uncertainty among clinicians in diagnosing dementia subtype, as those with a history of TBI were significantly less likely to be diagnosed with Probable AD and slightly more likely to be diagnosed with vascular dementia or corticobasal degeneration. TBI history was rarely judged by clinicians to be a causal factor in the development of dementia, suggesting that if TBI history was known it was seldom taken into account by the clinicians making dementia diagnoses.

The high social cost of TBI has stimulated substantial investments from both public and private sectors to develop effective therapies to limit neurodegeneration, foster neurological repair, and facilitate rehabilitation interventions post TBI. The last two decades have witnessed major advances in understanding the pathophysiology of TBI, as well as significant success in ameliorating trauma-induced neurodegeneration in animal models. However, well-done Phase III clinical trials of several of these therapies have failed to demonstrate efficacy (Doppenberg & Bullock, 1997), as have many clinical trials of rehabilitation interventions (Saatman et al., 2008). Similarly, major advances in the study of dementia and AD in particular have resulted in the development of behavioral, pharmacological, and surgical interventions, but identification of an effective disease-modifying intervention remains an elusive goal in AD research. For older adults in particular, an important barrier to successful intervention may be that our current level of understanding of dementia may group distinct disease processes (e.g., beta amyloid disease, tauopathy, and long-effects of a TBI) under one label (e.g., "AD"). Clinical trials are likely to be unsuccessful in identifying an effective intervention if people with different diseases are grouped together. Failure to consider TBI history in dementia diagnostics may preclude accurate attribution, diagnosis, and treatment of symptoms.

This study has limitations that should be considered. First, the study sample includes people with dementia without differentiation of the dementia type. This was important to the questions being addressed as it allowed the variance among clinical scales to be maximized. However, it may be informative to study the cognitive phenotype of dementia with and without TBI by dementia type (e.g., Probable AD, Dementia with Lewy Bodies). By the same token, it is possible that TBI results in accelerated functional decline that does not lead to a dementia-like condition. Full characterization of aging after TBI is not possible in the current study. Second, the quality of information about TBI history, severity, and overall clinical characterization of TBI was limited in the current study. TBI history was gathered by report of self or caregiver with medical record verification only when relevant medical records were available. Recall bias is an inherent limitation of such retrospective data collection. This problem is somewhat ameliorated by the fact that only "TBI with extended LOC" or "TBI with chronic deficit or dysfunction" was considered, as recall bias is less likely with an injury that resulted in LOC or chronic disability. However, it is possible some of the individuals in the group of dementia without TBI group had experienced past TBI without significant injury such they did not think to report it. Moreover, the NACC dataset does not contain information regarding the time from TBI to the onset of dementia. In cases of short onset time, the TBI may be a consequence of the preclinical stages of the neurodegenerative disease. It is also possible that clinical symptoms in those with TBI may represent unresolved TBI-related deficits and not a dementing condition. Additional covariates of interest, such as gender, genetic factors, and injury severity, should be addressed with a larger sample. Further longitudinal research is necessary to evaluate progression of changes along several functional domains among individuals with dementia who do and do not have a history of TBI.

The current study also has strengths that warrant consideration. The NACC database provides a rich resource of systematically collected uniform data points on a large and diverse sample of older adults. Data are gathered through many sources, including clinician ratings of symptoms and signs during memory clinic visits, a focused neuropsychological battery, medical record review, subject self-report, and informant report (Morris et al., 2006). The breadth of these assessments allows for comprehensive investigation of multiple aspects of health and functioning. The use of research-quality clinical or consensus-based dementia diagnostic criteria (e.g., (McKhann et al., 1984)) across ADCs is another strength of this and other studies using the NACC database. Moreover, the fact that TBI history does not appear to be thoroughly considered in standard consensus-based dementia diagnostics lends some credibility to the findings reported here, as clinicians were not biased to search for unique clinical features in subjects with known TBI history.

The findings of the current study suggest that dementia among individuals with a history of TBI may represent a unique clinical phenotype that is distinct from that seen among individuals who develop dementia without a history of TBI. The extent to which these clinical features represent chronic consequences of TBI or a unique post-TBI dementing process warrants further investigation. Because the ideal dataset to systematically evaluate post-TBI degeneration does not yet exist, knowledge can be advanced in the short term by characterizing clinical dementia symptoms among individuals with a history of TBI using existing data resources.

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Table 1

Demographic information for cases and controls

	Cases with dementia and TBI (*n* = 321)	Cases with dementia and no TBI (*n* = 654)	*p*
Gender (% Male)	67.0%	45.3%	0.000
Age (y) at initial evaluation (mean (SD))	72.0 (10.8)	69.2 (10.6)	0.001
Education (y; mean (SD))	13.9 (3.6)	13.9 (3.6)	0.780
Ethnicity (% Caucasian)	86.4%	82.6%	0.440

Table 2

Cognitive functioning among cases and controls

Test	Cases with dementia and TBI (mean rank)	Cases with dementia and no TBI (mean rank)	Mann-Whitney *U*	*p*	Effect size ($r = Z/\sqrt{N}$)
MMSE[1]	492.58	452.99	87491.5	0.035	0.07
Logical Memory IA	434.46	387.11	64880.0	0.006*	0.10
Logical Memory IIA	431.28	379.70	61984.5	0.001*	0.11
Category Fluency (Animals)	452.23	407.81	71894.0	0.012*	0.09
Trails A	362.41	385.21	59774.0	0.173	–
Trails A (# correct lines)	167.73	154.49	10343.0	0.063	–
Trails B	265.23	293.69	32467.5	0.043	0.09
Trails B (# correct lines)	131.77	113.26	5588.0	0.025	0.15
Boston Naming Test	415.52	406.38	73510.5	0.600	–
Test	Cases with dementia and TBI (mean (SD))	Cases with dementia and no TBI (mean (SD))	*t*(df)	*P*	Cohen's *d*
WAIS-R[2] Digit Symbol	24.65 (12.41)	23.91 (14.55)	0.598 (473)	0.550	–
Digit Span Forward	6.46 (2.45)	6.51 (2.43)	0.249 (561)	0.804	–
Digit Span Backward	4.18 (2.52)	4.04 (2.07)	0.764 (556)	0.445	–

*$p \leq 0.012$.

[1]MMSE = Mini Mental State Examination.

[2]WAIS-R = Wechsler Adult Intelligence Scale, Revised.

Table 3

Psychiatric functioning among cases and controls

Measure	**Cases with dementia and TBI (mean rank)**	**Cases with dementia and no TBI (mean rank)**	**Mann-Whitney *U***	***p***
Geriatric Depression Scale (GDS)	461.70	453.86	91271.5	0.669
Neuropsychiatric Inventory (NPI-Q)	505.19	461.40	91234.5	0.020 *
Measure	Cases with dementia and TBI (% of cases)	Cases with dementia and no TBI (% of cases)	*Fisher's Exact Test*	*p*
Depressive disorder (past 2 years)	49.2%	43.1%	–	0.069
Depressive disorder (>2 years ago)	25.1%	18.6%	–	0.060

* $p < 0.05$.

Table 4

Overall health among cases and controls

Measure	**Cases with dementia and TBI (mean rank)**	**Cases with dementia and no TBI (mean rank)**	**Mann-Whitney *U***	***p***
Cardiovascular health	510.98	483.39	101081.5	0.018*
Cerebrovascular health	500.30	481.35	99920.5	0.002*
Medical/metabolic health	507.21	482.82	101920.5	0.180
Number of medications	522.87	477.32	97623.5	0.017*
Measure	Cases with dementia and TBI (% of cases)	Cases with dementia and no TBI (% of cases)	*Pearson Chi Square*	*p*
Clinically significant alcohol abuse (active)	3.4%	1.2%	3.88	0.274
Clinically significant substance abuse (active)	2.2%	2.7%	0.468	0.926
Cigarette smoking (past 30 days)	5.0%	4.9%	0.14	0.932

*$p < 0.021$.

Table 5

Dementia diagnosis subtypes among cases and controls

Measure	Cases with dementia and TBI (*n* (%) of cases)	Cases with dementia and no TBI (*n* (%) of cases)	*Fisher's Exact test*	*p*
Consensus diagnosis of Probable AD	170 (45.1%)	207 (55.9%)	–	0.005 *
Clinical Diagnosis of Dementia with Lewy Bodies	26 (8.1%)	20 (6.1%)	–	0.203
NINDS/AIREN [1] Diagnosis of Vascular Dementia	16 (5.0%)	7 (2.1%)	–	0.040
DSM-IV Diagnosis of Alcohol-related dementia	8 (2.5%)	2 (0.6%)	–	0.050
Clinical Diagnosis of Frontotemporal Lobar Degeneration	35 (10.9%)	39 (11.9%)	–	0.388
Clinical Diagnosis of Primary Progressive Aphasia	22 (6.9%)	21 (6.4%)	–	0.475
Clinical Diagnosis of Corticobasal Degeneration	12 (3.7%)	4 (1.2%)	–	0.034

* $p < 0.017$.

[1] NINDS/AIREN = National Institutes of Neurological Disorders and Stroke/ Association Internationale pour la Recherché et l'Enseignement.