



History of Traumatic Brain Injuries in an Outpatient Clinic Sample Evaluated for Neurocognitive Disorders: A Retrospective Analysis

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Abstract

Objective: Prior traumatic brain injury (TBI) may increase the risk for neurocognitive disorders (NCD). However, research is equivocal and suggests other factors, such as psychiatric symptoms, may contribute. The primary aim of this study was to characterize the frequency of prior TBI in a population with suspicion of NCD. The secondary aim was to examine the relationships of prior TBI in relation to NCD diagnosis. **Methods:** A retrospective analysis was conducted in a sample of treatment-seeking adults (N=135) evaluated for suspicion of NCD at an outpatient neuropsychology clinic over a 13-month period (2021-2022). Prior TBI and mental health history were assessed during a clinical interview. Diagnosis of NCD was based on DSM-5 criteria. Generalized linear modeling and robust analysis of covariance were used to assess relationships between prior TBI and NCD diagnosis. **Results:** Two-thirds of patients (n=91) reported at least one prior TBI and 20% (n=18) of those patients denied prior evaluation or treatment for their most severe TBI. Fifty-two percent of patients (n=70) met criteria for a NCD and 17% of patients (n=23) met criteria for NCD due to TBI. Prior TBI did not predict NCD diagnosis. An interaction was identified, with prior psychiatric diagnosis and prior TBI differentially related to type of NCD (Q=6.29, p=0.02). **Conclusion:** Prior TBIs were frequently reported in patients seeking outpatient neuropsychological evaluations for cognitive concerns. Prior TBI did not predict NCD diagnosis.

Keywords: Traumatic brain injury; Neurocognitive disorder; Dementia; Head injury; Cognitive decline; Trauma prevention; Primary care

Introduction

Traumatic brain injury (TBI) is a significant public health concern, with 4.8 million people in the United States (US) evaluated for TBI in an Emergency Department (ED) annually [1]. TBIs often result from serious events involving an impact to the head, such as falls, motor vehicle crashes, or sports injuries [1-3]. While individuals may seek medical evaluation after the event, a significant number of people do not seek medical care, especially if the event was considered "minor," the injury occurred at home, or the individuals lack access to appropriate health services, such as in rural or high-poverty areas [4-6].

Background

TBIs range in severity from mild to severe, but the most common type is mild TBI (mTBI). Symptoms associated with mTBI (e.g., altered levels of consciousness, headaches, or change in sleep and mood) are typically transient and patients typically recover within 6-12 months [1,7-9]. However, some patients with mTBI may experience persistent changes in functional and cognitive abilities, which can result in a diagnosis of a neurocognitive disorder (NCD) [3,8,10-14].

A NCD is a change in cognitive ability from baseline functioning that is not attributable to normal aging, acute delirium, or other mental health disorder [15,16]. A mild NCD does not significantly interfere with the ability to independently complete basic or instrumental activities of daily living (ADLs; such as driving, preparing meals, managing medication); whereas individuals with major NCD require assistance completing at least one ADL. Additionally, there are several etiologies of NCDs, such as NCD due to Alzheimer's disease, vascular dementia, or traumatic brain injury (NCD+TBI) [16]. To meet criteria for NCD+TBI, individuals must meet criteria for mild or major NCD and the decline must be attributed to a known TBI with symptoms persisting after the brain had time to heal [16].

Prior research suggests that history of TBI may increase risk for developing major NCD later in life (e.g., NCD due to Alzheimer's or vascular disease) [17]. A recent meta-analysis reported that individuals with previous mTBI were 1.96 times more likely to be diagnosed with major NCD, [18] and a robust longitudinal study found that individuals with a single head injury, which can include TBI, had 1.25 times increased risk in developing a major NCD, with higher association among females and white participants [19,20]. Comparatively, other studies indicate that secondary factors, such as psychiatric symptoms, health comorbidities, or

demographic and clinical factors other than prior TBI, increase risk for NCD [15,21-23]. It is a challenge to tease apart the long-term effects of TBIs on neurocognitive changes because many TBI symptoms are also symptoms of NCD, and timely recognition and treatment may be hindered by lack of access to ambulatory and mental health services in non-urban areas [5,24-27]. Much of the current research on TBIs has been conducted in large academic trauma centers, with limited research in treatment-seeking populations.

The primary aim of this study was to characterize the frequency of prior TBI in a population of treatment-seeking patients who report symptoms of cognitive decline. The secondary aim was to examine the relationships of prior TBI on diagnosis of NCD. While prior research has been mixed, we hypothesized that history of TBI would increase the likelihood of NCD diagnosis and that patients with prior TBI would have higher incidence of NCD+TBI diagnosis versus a general NCD diagnosis or no NCD diagnosis.

Methods

Data Source and Participants

The current study was a retrospective analysis of a clinical sample of adults referred to an outpatient neuropsychology clinic in the western United States (n=135). Primary reasons for referral included suspicion of neurodegenerative disorder (i.e., dementia, multiple sclerosis, Huntington's disease), NCD due to TBI or cerebrovascular insult (i.e., stroke), or attention deficit hyperactivity disorder (ADHD). All patients previously completed a clinical interview and neuropsychological testing, and diagnoses were documented in the electronic medical record (EMR), which was available for record review. Evaluations were conducted by a single clinician between September 2021 and October 2022. Data collection included retrospective review of the medical record and clinical notes from the evaluation. Because data were collected retrospectively, the requirement of informed consent was waived by the institutional review board.

Study Design and Study Variables

Clinical Interview: The clinical interview lasted between 1-2 hours and, when possible, also included collateral report from an individual who knew the patient well, such as a family member. The interview included a review of current cognitive concerns and associated changes in overall functioning. Patients provided their medical, psychiatric, educational, and occupational history. Demographic variables included age at time of exam, biological sex, and years of education. Medical comorbidities assessed during the clinical interview and confirmed via chart review included cardiometabolic disorders, neurologic disorders, prior COVID-19 infection, and neurodevelopmental disorders. Psychiatric symptoms included previously documented psychiatric disorders and current psychiatric medication use, which were ascertained through self-report and medical record review.

Self-report of prior TBI was ascertained during the clinical interview. Patients were asked if they had previously

sustained a head injury or experienced a time in which they "hit their head and felt dazed or confused afterwards." If patients answered yes, they were asked additional follow-up questions to better characterize the nature and sequelae of the injury. These variables were included in analyses as dummy variables: loss of consciousness (LOC); post-traumatic amnesia; altered consciousness or feeling dazed or confused; post-concussive symptoms such as changes in vision or hearing, headaches, nausea or vomiting, or feeling off balance; changes in thinking or memory; and if the patient received evaluation or treatment for the injury. Patients reported the total number of prior TBIs, but the current analysis includes information from the worst or most severe head injury (the "index" head injury), as reported by the patient. Severity of TBI (mild or severe) was determined by report of LOC and post-traumatic amnesia.

Neuropsychological Exam: Cognitive testing lasted 2-3 hours, with the primary goal of assessing current level of neuropsychological ability and differential diagnosis of NCD. Neuropsychological batteries included assessment of premorbid function, intellectual abilities, processing speed, attention, executive functioning, language, visuospatial abilities, learning, and memory. The Test of Premorbid Functioning (ToPF) was used to assess cognitive decline relative to baseline ability [28]. Performance validity was assessed for all patients using embedded measures of effort (WAIS-IV reliable digit span, CVLT-III), and, for some patients, a stand-alone measure of effort (Test of Memory Malingering). Names of tests, the number of patients who completed each test, and detailed analysis of neuropsychological data is found in Appendix A. While results of performance validity testing may have varied for some patients, no patients were suspected of malingering or thought to be providing suboptimal effort during test administration. Upon review of neuropsychological reports, all test results were thought to be an accurate reflection of the patient's current level of cognitive ability.

NCD diagnosis was based on DSM-5 criteria [16]. Diagnosis of NCD included a mild or major NCD of any kind. To meet diagnostic criteria, patients had to exhibit a decline in cognitive functioning in at least one cognitive domain relative to their baseline abilities (ToPF score) or cognitive impairment in addition to reported cognitive decline based on collateral report or documented decline based on medical chart review. Diagnosis of NCD due to TBI (NCD+TBI) was defined as a mild or major NCD specifically attributed to a history of TBI.

Statistical Analysis

All data analyses were completed using R statistical software (version 4.2.3) and R Studio (version 2023.03). Robust, non-parametric analyses were employed to limit the impact of non-normally distributed data and a relatively small sample size [29]. Missing data were removed from analyses at each step (for example, if patients were missing data on LOC they were not included in LOC analyses). Descriptive statistics were calculated for demographic and clinical characteristics; frequencies and percents are reported for categorical variables and medians and mean absolute deviations (MAD) are reported for continuous variables.

A generalized logistic regression model (glm command, family = binomial) was used to predict the likelihood of NCD diagnosis based on TBI history. Patient age was included in all models and a stepwise approach was used to explore if prior TBI and other aspects of the TBI related to diagnosis of NCD, including LOC, number of prior TBIs, and treatment for TBI. To compare goodness of fit between models, Akaike information criterion (AIC) and Hosmer-Lemeshow tests (using the 'ResourceSelection' package in R) were conducted.

To compare the predictive main effects and interactions of prior psychiatric diagnosis on type of NCD diagnosis (NCD versus NCD+TBI), robust analysis of covariance was used (ranova command, using the Walrus package in R) with a method of trimmed means (tr=0.2). Analyses were adjusted for multiple comparisons to limit the influence of Type II Error. Given that two sets of analyses were conducted (assessment for any type of NCD and assessment for NCD+ TBI), results were considered significant at an alpha-level of 0.025.

Results

Prior TBI in the Current Sample

As shown in Table 1, 91 patients (67%) reported at least one prior TBI. Among patients with a prior TBI, 41 patients (45%) reported a single TBI, and 50 patients (55%) reported multiple TBIs. The most common cause of injury was falls, followed by motor vehicle crashes. Of the patients who endorsed LOC with the index TBI, and could quantify its duration (n=21), 14 patients (67%) reported LOC of less than 5 minutes. Eighty-four percent of TBIs were classified as mild. Twenty percent of patients denied receiving evaluation and treatment for the injury.

When comparing patients with and without a history of TBI, there were no significant differences in cardiometabolic, neurologic, or psychiatric disorders, COVID-19 infections, or use of psychiatric medications (all p values > 0.10). Patients with a TBI history had a higher rate of documented psychiatric diagnoses compared to those without a history of TBI (68% vs. 32%), but the difference was not statistically significant (p=0.94).

Diagnosis of Neurocognitive Disorder

Forty-eight percent of patients (n=65) did not meet criteria for a NCD diagnosis, whereas 52% of patients (n=70) met clinical criteria for any NCD (Table 2). Among patients diagnosed with NCD, 41 patients (59%) met criteria for mild NCD and 29 patients (41%) met criteria for major NCD. Patients with any NCD were significantly older than patients without NCD (73 vs. 43 years, p<0.01). There were no statistically significant differences between those with and without an NCD diagnosis in medical comorbidities,

psychiatric diagnosis, or prior TBI (all p values>0.10). Twenty-three patients (17% of study sample or 33% of NCD patients) met criteria for NCD+TBI.

Predicting Neurocognitive Disorder

Regression analyses are summarized in Table 3. Age significantly predicted NCD diagnosis in all models, with older patients being more likely to be diagnosed with NCD compared to younger patients. Prior TBI, LOC, number of prior TBIs, and treatment for TBI were not associated with NCD diagnosis in any model. When the relationship between TBI and type of NCD diagnosis was explored, neither the main effect for psychiatric diagnosis nor the main effect for prior TBI related to NCD diagnosis. The interaction between prior psychiatric diagnosis and prior TBI significantly predicted NCD diagnostic group (Q=6.29, p=0.02).

	History of TBI (N=91)
Cause of Injury, n (%)	
Fall	42 (46%)
Motor Vehicle Crash	14 (15%)
Sports-Related	7 (8%)
Physical Assault	10 (11%)
Other	17 (19%)
Classification of TBI	
Mild	76 (84%)
Severe	15 (16%)
Loss of Consciousness (LOC), n (%)	
Endorsed	39 (43%)
No LOC	37 (41%)
Unsure	1 (1%)
Missing Data	14 (15%)
Duration of LOC, n (%)*	
Less than 5 minutes	14 (67%)
5-30 Minutes	3 (14%)
> 30 Minutes	2 (10%)
Posttraumatic Amnesia (PTA), n (%)	26 (29%)
Post-Concussive Syndrome (PCS), n (%)	47 (52%)
Prior TBI Reported with Referral, n (%)	22 (24%)
Number of Prior TBIs, n (%)	
Single	41 (45%)
Multiple (2-7)	50 (55%)
Evaluation/Treatment after Injury, n (%)	
Yes	58 (64%)
No	18 (20%)
Unknown	15 (16%)

*Reported from participants who reported a LOC and could recall the duration (n=21).

Table 1: Injury Characteristics for Participants Reporting Prior Traumatic Brain Injury (TBI) (N=91).

	Total Group (N=135)	No NCD (N=65)	Any NCD (N=70)	p-value
Age in Years, median (MAD)	61 (25)	43 (24)	73 (14)	<0.01*
Female, n (%)	82 (61%)	42 (65%)	40 (57%)	0.47
White, n (%)	113 (94%)	62 (95%)	67 (96%)	0.74
Years of Education, median (MAD)	14 (3)	14 (3)	13 (1.5)	0.13
Medical Comorbidities, n (%)				
Cardiometabolic Disorder	67 (50%)	27 (42%)	40 (57%)	0.10
Neurological Disorder	74 (55%)	36 (55%)	38 (54%)	>0.99
COVID-19 Infection	44 (33%)	22 (34%)	22 (31%)	0.95
Neurodevelopmental Diagnosis	20 (15%)	9 (14%)	11 (16%)	0.95
Psychiatric Diagnosis, n (%)				
Prior Psychiatric Diagnosis, n (%)	93 (69%)	49 (75%)	44 (63%)	0.17
Current Psychiatric Medication, n (%)	57 (42%)	31 (48%)	26 (37%)	0.32
Prior Traumatic Brain Injury (TBI), n (%)	91 (67%)	45 (69%)	46 (66%)	0.80

*Significant at $p < 0.001$

Table 2: Demographic Characteristics and Medical History of the Sample, Compared by Diagnosis of Neurocognitive Disorder (NCD) (N=135).

	Model 1		Model 2		Model 3		Model 4	
	β	p-value	β	p-value	β	p-value	β	p-value
Age	0.04	<0.01**	0.03	<0.01*	0.03	<0.01**	0.03	0.01*
Prior Traumatic Brain Injury (TBI)	< -0.01	1.00						
Loss of Consciousness (Missing cases N=58)			0.43	0.39				
Number of Prior TBIs					0.46	0.30		
Treatment for TBI (Missing cases N=58)							< 0.01	1.00
Hosmer and Lemeshow X^2	13.78	0.09	6.13	0.63	2.91	0.99	6.68	0.57
Akaike Information Criterion (AIC)	174.74		104.75		122.83		105.69	

** Significant at $p = 0.001$

Notes: The estimates for prior head injury were not estimable when LOC were entered into the model. Plausible explanations are included in the results and discussion section.

Table 3: Logistic Regression Results Predicting Any Type of Neurocognitive Disorder (NCD; Total N=135; NCD n=70).

Discussion

It is estimated that more than one-quarter of adults have experienced at least one TBI [30,31]. In the present study of patients referred to an outpatient neuropsychological clinic for cognitive evaluation, two-thirds of patients self-reported at least one prior TBI, which is significantly higher than base-rates reported in other studies [32]. Incidence of prior TBI did not differ for patients diagnosed with or without NCD.

Twenty percent of patients reporting a prior TBI indicated that they did not seek evaluation or treatment for the injury. This underscores the importance of providers in primary care and outpatient clinic settings routinely assessing their patients for prior TBI experiences. Assessing TBIs retrospectively is challenging for providers, as patients have a difficult time recalling if they experienced post-concussive symptoms like LOC and how long those symptoms lasted. However, regular assessment of TBI as part of routine wellness exams is strongly recommended, as that historic record can be particularly critical when providers are evaluating whether new changes in mental status are due to aging, infection, delirium, or other causes. Noting that one-

fifth of patients with a prior TBI did not seek treatment for their injury, it is also essential to equip primary care providers and patients with information on normal and atypical TBI recovery trajectories and evidence-based treatment recommendations, such as increased rest before resuming normal activities and limiting alcohol intake [5,8,33,34].

A secondary aim of this study was to explore if prior TBI was associated with NCD diagnosis. Results suggest patients with prior TBIs were equally likely as those without prior TBIs to develop NCD. When exploring this relationship by type of NCD, interaction effects were identified between prior psychiatric diagnosis and history of TBI. Additional work is warranted to better specify characteristics and causal pathways between TBI and psychiatric diagnosis as they relate to NCD.

One of the unique strengths of the study was the method for assessment of NCD. Prior research has primarily relied on identification of NCD from medical record chart review or death certificates or from brief prospective cognitive screeners meant to assess for the possibility of impairment (as opposed to providing a definitive diagnosis) [14,35]. The current study utilized prospective neuropsychological evaluation conducted explicitly to assess

and diagnose cognitive functioning. While there are challenges with administering standardized testing in clinical settings, the flexible design adds strength to the study because each patient was assessed appropriate to their cognitive abilities and testing could be administered more flexibly to minimize burden to the patient and to accommodate medical conditions or impairments that impact testing (color blindness, hearing impairment, testing fatigue, pain, etc.). All study patients received similar batteries and testing experiences (i.e., same testing environment, testing conducted by the same provider, assessment of similar cognitive domains); however, specific testing batteries and duration of test administration were patient dependent.

Limitations

The study has several limitations. First, sample size was relatively small and group sizes were not equal, which may have limited the ability to detect smaller effects and precluded more powerful statistical approaches. However, robust statistical analyses were employed to help limit effects of unequal sample sizes. Second, the study sample was comprised of individuals referred for neuropsychological evaluation, and potential selection bias should be considered when interpreting study results. Additionally, individuals with mTBI (as opposed to more severe TBIs) may have been more likely to present for an outpatient evaluation. While the vast majority of TBIs were classified as mild (84%), this sample did include patients with more severe injuries. Finally, while patients were prospectively assessed for NCD during the clinical exam, many variables were ascertained from retrospective chart review. Uniform data were not available on all TBIs, including date of injury, and self-report of symptoms may be unreliable, especially in a population of patients with cognitive concerns that necessitated the evaluation.

Conclusion

Adults in an outpatient clinic setting endorsed a high rate of prior TBIs, and 20% of those TBI events were untreated. Findings underscore the importance of assessing for TBIs in primary care settings so early detection and treatment can potentially mitigate development of neurocognitive disorders.

Conflicts of Interest

Dr. Clausen received compensation for her work as data analyst and lead author. Dr. Clausen has no other financial conflicts of interest to report. Ms. Spilman received compensation for her work as a medical writing and research consultant. Ms. Spilman has no other financial conflicts of interest to report. Ms. Meyers has no other financial conflicts of interest to report.

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