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Authors

Gardner, Raquel C
Peltz, Carrie B
Kenney, Kimbra
et al.

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Research Article

Remote Traumatic Brain Injury Is Associated with Motor Dysfunction in Older Military Veterans

Raquel C. Gardner,[1,2] Carrie B. Peltz,[2] Kimbra Kenney,[3] Kenneth E. Covinsky,[2,4] Ramon Diaz-Arrastia,[3] and Kristine Yaffe[1,2,5,6]

[1]Memory and Aging Center, Department of Neurology, University of California San Francisco. [2]San Francisco Veterans Affairs Medical Center, California. [3]Department of Neurology, Uniformed Services University of the Health Sciences, Bethesda, Maryland. [4]Division of Geriatrics, [5]Department of Psychiatry, and [6]Department of Epidemiology and Biostatistics, University of California San Francisco.

Address correspondence to Raquel C. Gardner, MD, Department of Neurology, University of California San Francisco, 4150 Clement Street, San Francisco, CA 94121. E-mail: raquel.gardner@ucsf.edu

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Abstract

Background: Traumatic brain injury (TBI) has been identified as a risk factor for Parkinson's disease (PD). Motor dysfunction among TBI-exposed elders without PD has not been well characterized. We sought to determine whether remote TBI is a risk factor for motor dysfunction on exam and functionally relevant motor dysfunction in day-to-day life among independently living elders without PD.

Methods: This is a cross-sectional cohort study of independently living retired military veterans aged 50 or older with (n = 78) and without (n = 85) prior TBI—all without diagnosed PD. To characterize multidimensional aspects of motor function on exam, the Unified Parkinson's Disease Rating Scale (UPDRS) Motor Examination was performed by a board-certified neurologist and used to calculate a modified UPDRS (mUPDRS) global motor score and four domain scores (tremor, rigidity, bradykinesia, and posture/gait). Functionally relevant motor dysfunction was assessed via self-report of falls within the past year.

Results: In analyses adjusted for demographics and comorbidities that differed between groups, compared with veterans without TBI, those with moderate-to-severe TBI were more likely to have fallen in past year (33% vs. 14%, risk ratio 2.5 [95% confidence interval 1.1–5.4]), had higher (worse) mUPDRS global motor (p = .03) and posture/gait scores (p = .02), but not higher tremor (p = .70), rigidity (p = .21), or bradykinesia scores (p = .22). Mild TBI was not associated with worse motor function.

Conclusions: Remote moderate-to-severe TBI is a risk factor for motor dysfunction—defined as recent falls and impaired posture/gait—among older veterans. TBI-exposed older adults may be ideal candidates for aggressive fall-screening and prevention strategies.

Keywords: Falls—Parkinson's disease—Risk factors

Traumatic brain injury (TBI) is extremely common across the life span, with an estimated lifetime prevalence of more than 40% in adults (1). 2.5 million Americans seek medical attention for TBI annually (2) and many more sustain TBI but do not seek care (3). TBI is particularly common among military veterans, in whom incidence is estimated to be 8–44 times that of civilians (4). TBI may lead to immediate motor dysfunction via traumatic injury to brain regions subserving motor function (5). TBI has also been identified as a risk factor for later development of progressive neurodegeneration and motor dysfunction in the form of Parkinson's disease (PD) (6–8).

Prevalence of PD is relatively low in the general population, affecting less than 1% of adults aged 50 or older and less than 2.5% of adults aged 80 or older (9). However, aging-related "mild parkinsonian signs" manifesting as tremor, rigidity, bradykinesia, or posture/gait disturbance of insufficient severity to warrant a diagnosis of PD are common. The prevalence of mild parkinsonian signs increases with age and has been reported in up to half of community-dwelling older adults aged 85 years and older without a clinical diagnosis of PD (10). Although these mild parkinsonian signs rarely meet criteria for PD, they can nevertheless be progressive and have been associated with increased mortality and heightened risk of a number

of negative health outcomes including falls (10–12). Most importantly, mild parkinsonian signs have been associated with increased functional disability and loss of independence among older adults (13,14).

Despite their high prevalence and associated impact on function and independence, risk factors and mechanisms for aging-related mild parkinsonian signs are poorly understood and effective treatments do not exist.

Furthermore, although mild parkinsonian signs are classically viewed as being due to dysfunction in the dopaminergic motor system, there are many other systems (vestibular, autonomic, and musculoskeletal) that may also be impacted by TBI and may produce findings that overlap with the parkinsonian sign complex.

Thus, whether remote TBI is a risk factor for motor dysfunction among older adults without PD has important public health implications. Our aim in this study was to determine whether remote TBI is a risk factor for both objective motor dysfunction on exam (defined as mild parkinsonian signs) and subjective functionally relevant motor dysfunction (defined as self-reported falls) among older independently living military veterans without PD. We chose to study older military veterans because this is a large and growing population—representing 50% of American men older than 65 years (15)—that is enriched for TBI exposure and therefore may be at particularly high risk for chronic disabling sequelae of TBI.

Methods

Design and Protocol Approval

This is a cross-sectional cohort study. The study was approved by the Human Research Committees at both sites. Written informed consent was obtained from all participants.

Study Population

Participants aged 50–95 years were recruited from independently living residents of the Armed Forces Retirement Home (AFRH; Washington, DC) and Veterans Home of California–Yountville (VHCY; Yountville, CA). In order to gain admission to these retirement communities, residents must be U.S. military veterans and must be functionally independent (ie, able to manage medications, appointments, laundry, etc.), live in a communal environment, and not engage in active substance abuse. After admission, the homes are able to provide accommodation until the end of life with gradually increasing levels of assistance on an as-needed basis. For this study of high-functioning older adults, we recruited only from the fully independent sections of these retirement communities. We additionally excluded individuals with low cognition (Mini-Mental State Examination (16) [MMSE] < 20), past penetrating head injury, pre-existing diagnosis of PD, or medical conditions severe enough to limit assessment of motor outcomes (eg, bilateral leg amputation, advanced myotonic dystrophy, or childhood polio). Participants were enrolled between July 2013 and May 2016.

TBI Exposure

TBI exposure was determined using the Ohio State University TBI Identification method (17) (OSU-TBI-ID), a detailed semi-structured in-person interview that ascertains self-reported history of prior TBI including the cause, timing, and associated symptoms of each reported TBI. The OSU-TBI-ID is a National Institute for Neurological Disorders and Stroke (NINDS) recommended TBI Common Data Element (18) (CDE) and is considered a gold standard measure for self-report of TBI. "TBI" was defined as a prior history of at least one head injury that occurred greater than 2 years ago, produced neurological symptoms, and necessitated medical attention. "No-TBI" was defined as no prior history of any head injury that produced neurological symptoms or necessitated medical attention. Although medical record verification of TBI at the time of injury was not feasible, TBI history was confirmed in 38% of TBI veterans via review of retirement home charts. None of the no-TBI veterans had a TBI recorded in their chart.

TBI Features

The following TBI features were recorded based on responses to the OSU-TBI-ID: number of prior TBIs, history of TBI with loss of consciousness (LOC), time since first TBI, time since most recent TBI, and TBI severity. A TBI was considered mild if there was LOC for zero to less than 30 minutes (19). A TBI was considered moderate/severe if there was LOC for 30 minutes or more. Given that most TBI participants reported more than one TBI, TBI severity for an individual participant was categorized based on the most severe TBI reported by that participant.

Assessments

All study participants underwent in-person assessment including medical history, assessment of global cognition and function (MMSE and Clinical Dementia Rating Scale (20) [CDR]), and assessment of physical activity level (Rapid Assessment of Physical Activity (21) [RAPA]). Most (54 TBI and 68 no-TBI) also underwent neurologic examination with the Unified Parkinson's Disease Rating Scale (22) [UPDRS] Motor Examination by a board-certified neurologist. Information was collected on age, gender, race, years of education, years in military, history of deployment, and baseline comorbidities (diabetes, hypertension, depression, anxiety, posttraumatic stress disorder [PTSD], prior substance abuse [including alcohol or illicit drugs], and prior tobacco smoking). Additional detailed cognitive, behavioral, and functional measures were obtained and are reported separately (23).

Motor Outcomes

Primary outcomes were (i) self-reported history of falls within the past year and (ii) modified UPDRS Motor Examination (mUPDRS) global score and domain scores. The mUPDRS global score and domain scores capture mild parkinsonian signs based on selected items from the UPDRS Motor Examination. The UPDRS Motor Examination is a structured neurologic examination that includes 27 individually scored items, with scores ranging from 0 (normal) to 4 (severely impaired). UPDRS Motor examinations were performed by licensed neurologists (R.C.G. and K.K.) who had undergone training in performing the UPDRS Motor examination. Efforts were made to blind the examiners to TBI status whenever possible, but this was frequently not achievable. Although the UPDRS Motor Examination was originally developed for use in patients with PD, it has been adapted and validated for use among older adults without PD in order to capture the multidimensional aspects of "mild parkinsonian signs" that so many older adults experience regardless of etiology (24). Based on factor analysis of UPDRS Motor Examination data from three large cohort studies of older adults without PD, a mUPDRS global score and four domain scores (capturing tremor, rigidity, bradykinesia, and posture/gait domains) may be calculated from selected UPDRS Motor Examination items and one additional item from the Consortium to Establish a Registry for Alzheimer's disease

(CERAD) exam (24). For our study, we used a slightly modified version of the mUPDRS scores based only on the UPDRS items. The four mUPDRS domain scores were calculated by summing points on the relevant UPDRS Motor Examination items, dividing by the maximum achievable points in that domain, and multiplying by 100 (thus generating a score ranging from 0 to 100 for each domain). Individual UPDRS Motor Examination items included in each mUPDRS domain score are as follows: tremor score (face tremor, action tremor of right and left hands, and resting tremor of right and left hands and feet), rigidity score (rigidity in the neck and each limb), bradykinesia score (right and left finger taps, right and left fist opening/closing, right and left rapid alternating hand movements, and right and left heel taps), and posture/gait score (arising from a chair, posture, gait, postural stability, and overall body bradykinesia/hypokinesia). The mUPDRS global score was calculated by averaging the four mUPDRS domain scores, resulting in a global score ranging from 0 to 100.

Statistical Analysis

Demographics and baseline characteristics were compared between TBI and no-TBI veterans using *t* tests for continuous variables or chi-square tests for categorical variables. Rate of falls in the past year and mUPDRS global motor and domain scores were compared between TBI and no-TBI veterans using linear regression for models of continuous outcomes and Poisson regression with a robust variance estimator to estimate risk ratios (RRs) for models of categorical outcomes (25). Regression models were adjusted for demographics and comorbidities that differed between groups at p less than .05 (age, sex, diabetes, depression history, substance abuse history, and site). Effects of TBI severity were assessed in models stratified according to TBI severity (none, mild, or moderate/severe TBI). Given that data were only available regarding falls within the past year, in order to reduce the likelihood that a participant's propensity to fall did not precede TBI, sensitivity analyses assessing risk of falls after TBI were performed after (i) excluding TBI veterans with first-reported TBI within the past 30 years and (ii) excluding TBI veterans with any TBI ever due to a fall. Significance was set at p less than .05.

Results

Characteristics of TBI and no-TBI veterans are shown in Table 1. TBI veterans were younger, less likely to be women, and more likely to have prior blast injury, ever boxed, diabetes, depression, and prior alcohol/drug abuse. Functional status and physical activity level

Table 1. Characteristics of Older Veterans With and Without Traumatic Brain Injury

Characteristics, Mean (*SD*) or %	No-TBI (n = 85)	TBI (n = 78)	p Value
Demographics			
Age (y)	79.4 (8.2)	76.4 (10.0)	.04
Male	82.4	94.9	.03
White	83.5	94.9	.08
Education (y)	14.5 (2.6)	14.2 (2.6)	.38
Military, boxing, and football exposure			
Years in military	11.1 (9.0)	10.9 (9.2)	.92
Deployed	77.7	74.4	.62
Any military blast-related injury	1.2	13.0	<.01
Ever boxed	11.1	25.0	.02
Ever played American football	35.8	45.3	.23
Baseline comorbidities			
Diabetes	21.2	37.2	.02
Hypertension	75.3	68.0	.30
Hyperlipidemia	65.9	62.8	.68
Depression	18.8	42.3	<.01
Anxiety	14.1	25.6	.06
PTSD	8.2	18.0	.06
Prior alcohol/drug abuse	17.7	38.5	<.01
Ever tobacco smoker	63.5	66.7	.68
Global function, cognition, and physical activity			
CDR sum of boxes	0.5 (0.7)	0.5 (0.9)	.86
MMSE	28.2 (1.5)	27.6 (2.5)	.04
Rapa1	3.5 (1.3)	3.5 (1.5)	.89
Rapa2	1.3 (1.4)	1.2 (1.4)	.82
TBI characteristics			
>1 TBI	NA	57.7	NA
Number of TBIs	NA	2.0 (1.2)	NA
% TBI with LOC	NA	76.9	NA
% Mild TBI	NA	65.4	NA
Years since first TBI	NA	53.2 (18.1)	NA
Years since last TBI	NA	37.0 (22.5)	NA
% Military-related TBI	NA	25.6	NA
% TBI due to a fall	NA	42.3	NA

Note: CDR = Clinical Dementia Rating Scale; LOC = loss of consciousness; MMSE = Mini-Mental Status Examination; Rapa1 = Rapid Assessment of Physical Activity 1; Rapa2 = Rapid Assessment of Physical Activity 2; PTSD = posttraumatic stress disorder.

were virtually identical between groups. Most TBI veterans reported sustaining a TBI greater than five decades ago: mean time since first TBI was 53 years (median 58 years).

Rate of recent falls was higher among TBI veterans (26%) versus no-TBI veterans (14%), and this difference reached trend-level significance (Table 2; unadjusted RR 1.82 [95% CI 0.95–3.47]; adjusted RR 1.70 [95% CI 0.88–3.28]). However, mean global motor score was not significantly different among TBI versus no-TBI veterans (mean (*SD*): 7.3 (5.9) vs. 8.6 (7.1); $p = .27$; adjusted mean (95% CI): 7.7 (6.1–9.2) vs. 8.1 (6.3–9.9); $p = .72$). Domain scores of tremor, rigidity, bradykinesia, and posture/gait were also not significantly different between TBI and no TBI veterans.

Stratification by TBI severity identified a dose–response such that veterans with moderate/severe TBI ($n = 27$), but not those with mild TBI ($n = 51$), had approximately 2.5 times higher risk of recent falls (adjusted RR 2.46 [95% CI 1.12–5.39]), and significantly higher global motor scores (adjusted mean 11.2 vs. 7.8, $p = .03$) compared with no TBI veterans (Tables 2 and 3). Analysis of domain scores revealed that the effect on global motor score was largely mediated by significantly higher scores in the posture/gait domain (adjusted mean 18.8 vs. 11.2, $p = .02$) but not in the tremor, rigidity, or bradykinesia domains among veterans with moderate/severe TBI versus no TBI veterans (Table 3).

Two sensitivity analyses of falls were conducted to mitigate the possibility that propensity for falls may have preceded TBI. In the first analysis, veterans with first TBI within the past 30 years were excluded ($n = 5$) and results were similar to the primary analysis (Table 2). In the second analysis, veterans with any TBI ever due to a fall were excluded ($n = 33$) and results were again similar to the primary analysis (Table 2).

Discussion

In this study of older, independently living U.S. military veterans with and without prior TBI, we found that very remote moderate/severe TBI, but not mild TBI, is associated with 2.5 times the risk of sustaining a fall within the past year and with greater posture/gait impairment on neurologic exam. Our conservative sensitivity analyses, designed to mitigate the possibility that propensity for falls preceded TBI, confirmed our primary results. Because all veterans in this study were functionally independent and did not have pre-existing diagnoses of PD, these findings suggest that even among otherwise high-functioning older veterans, very remote moderate/severe TBI may be a significant independent risk factor for functionally relevant motor dysfunction.

Although few prior studies have reported on domain-specific or functionally relevant details of motor function following very remote TBI, there is mounting evidence that TBI may be a risk factor for parkinsonian signs or PD. For example, severe TBI may occasionally produce immediate posttraumatic parkinsonism (26,27). Both mild and more severe TBI have been implicated as risk factors for Parkinson's disease (PD) (6,7), which may develop many years after TBI exposure. Others have reported an association between remote TBI and progression of parkinsonian signs on exam as well as Lewy body neuropathology (a hallmark feature of PD) at autopsy, though the functional relevance of these findings to patients was not reported (8). In addition, repeated subconcussive or concussive/mild TBI has been associated with CTE, a neurodegenerative tauopathy associated with progressive cognitive, behavioral, and motor deficits, including parkinsonism, usually many years after TBI exposure (28). At least one prior study has reported virtually no difference in prevalence of "head trauma" among older adults with and without mild parkinsonian signs as measured by the mUPDRS (29). Given the lack of determination of TBI or TBI severity in that study (which is not equivalent to "head trauma," a condition that may occur in the absence of brain trauma), it is difficult to interpret the results.

Mechanisms of aging-related mild parkinsonian signs are likely multifactorial and may include age-associated reductions in dopaminergic nigrostriatal activity, early stages of a neurodegenerative disease affecting the basal ganglia (such as PD), or the accrual of vascular disease in the brain (11). Interestingly, TBI may be an independent risk factor for each of these mechanisms (6,7,26,27,30). In our study, greater mild parkinsonian signs (as measured by the global motor score) among veterans with moderate/severe TBI appeared

Table 2. Falls in the Past Year According to Traumatic Brain Injury Severity

	Raw			Adjusted	
Falls in Past Year	% With Falls	RR Falls	95% CI	RR Falls	95% CI
Entire cohort					
No TBI ($n = 85$); Ref	14.1	—	—	—	—
Any TBI ($n = 78$)	25.6	1.82	0.95–3.47	1.70	0.88–3.28
Mild TBI ($n = 51$)	21.6	1.53	0.73–3.21	1.33	0.60–2.96
Mod/sev TBI ($n = 27$)	33.3	2.36	1.11–5.00*	2.46	1.12–5.39*
Excluding veterans with first TBI within past 30 years					
No TBI ($n = 85$); Ref	14.1	—	—	—	—
Any TBI ($n = 68$)	27.9	1.98	1.03–3.79	1.83	0.91–3.67
Mild TBI ($n = 45$)	24.4	1.73	0.83–3.61	1.46	0.64–3.33
Mod/sev TBI ($n = 23$)	34.8	2.46	1.14–5.32*	2.67	1.16–6.16*
Excluding veterans with any TBI due to a fall					
No TBI ($n = 85$); Ref	14.1	—	—	—	—
Any TBI ($n = 45$)	31.1	2.20	1.12–4.35	1.73	0.86–3.47
Mild TBI ($n = 31$)	29.0	2.06	0.96–4.41	1.56	0.69–3.50
Mod/sev TBI ($n = 14$)	35.7	2.53	1.05–6.10*	2.15	0.87–5.31

Notes: CI = confidence interval; Mod/sev = moderate/severe; Ref = reference value; RR = risk ratio. Adjusted model is adjusted for site, age, sex, diabetes, depression, and substance abuse.

*Significant at $p < .05$.

Table 3. Modified Unified Parkinson's Disease Rating Scale Motor Examination Scores According to Traumatic Brain Injury Severity

	Raw			Adjusted		
mUPDRS Scores	Mean	*SD*	*p*	Mean	95% CI	*p*
mUPDRS Global Score						
No TBI (*n* = 65); Ref	7.3	5.9	—	7.8	6.2–9.3	—
Mild TBI (*n* = 31)	7.5	6.5	0.89	6.0	3.7–8.2	0.21
Mod/sev TBI (*n* = 20)	10.4	7.8	0.06	11.2	8.5–13.9	0.03*
mUPDRS Tremor Score						
No TBI (*n* = 68); Ref	4.6	6.8	—	5.0	3.5–6.6	—
Mild TBI (*n* = 34)	4.0	6.4	0.65	2.8	0.5–5.2	0.14
Mod/sev TBI (*n* = 20)	5.2	5.8	0.74	5.7	2.8–8.6	0.70
mUPDRS Rigidity Score						
No TBI (*n* = 67); Ref	3.1	6.7	—	3.9	2.0–5.7	—
Mild TBI (*n* = 34)	3.7	5.9	0.75	1.6	–1.0 to 4.3	0.19
Mod/sev TBI (*n* = 20)	5.3	13.0	0.30	6.3	2.9–9.7	0.21
mUPDRS Bradykinesia Score						
No TBI (*n* = 67); Ref	10.6	10.0	—	11.0	8.6–13.4	—
Mild TBI (*n* = 33)	11.2	9.2	0.79	10.4	6.8–13.9	0.78
Mod/sev TBI (*n* = 20)	14.1	11.7	0.18	14.1	9.7–18.5	0.22
mUPDRS Posture/Gait Score						
No TBI (*n* = 67); Ref	11.0	11.5	—	11.2	8.3–14.1	—
Mild TBI (*n* = 32)	12.2	10.9	0.64	10.6	6.3–15.0	0.84
Mod/sev TBI (*n* = 20)	17.0	16.1	0.06	18.8	13.5–24.1	0.02*

Notes: CI = confidence interval; Mod/sev = moderate/severe; Ref = reference value; *SD* = standard deviation. Adjusted model is adjusted for site, age, sex, diabetes, depression, and substance abuse. All scores range from 0 (normal) to 100 (severely impaired).

*Significant at $p < .05$.

to be largely mediated by greater motor dysfunction only in the domain of posture/gait. The lack of greater impairment in the other three domains of tremor, rigidity, or bradykinesia suggests that the mechanisms of post-TBI motor dysfunction may be different from that of typical aging-relating "mild parkinsonian signs." We hypothesize that TBI-associated motor dysfunction may preferentially affect those nigrostriatal pathways specifically subserving posture/gait or may result from injury to entirely different systems including vestibular, autonomic, cerebellar, or musculoskeletal (31,32). Ultimately, ongoing and future prospective longitudinal studies of the chronic effects of TBI that incorporate detailed clinical phenotyping along with neuroimaging and body fluid biomarkers will be critical to determine underlying mechanisms and whether TBI-associated motor dysfunction is static or progressive over time.

Strengths of this study include the detailed in-person evaluations, the use of a functionally relevant patient-centered outcome (falls), highly granular motor evaluations down to the individual motor domain level (mUPDRS global and domain scores), use of a gold standard measure of lifetime TBI exposure (the OSU-TBI-ID), and corroboration of TBI history via chart review whenever possible. Additionally, although this study included only veterans, it is important to note that approximately 75% of reported TBIs occurred during civilian life, suggesting that our findings may be more widely generalizable. A limitation of this study is its cross-sectional design that precludes our ability to determine whether the identified motor dysfunction is static or progressive. Although reliance on self-report of TBI in this study was unlikely to have led to bias in the reported outcomes, self-report of duration of LOC could have led to misclassification of TBI severity if those with more severe TBI were less likely to accurately recall LOC duration. The lack of consistent blinding of examiners to TBI status of participants could have led to bias in the motor examination. Sample size was small and possibly underpowered to detect small effect sizes. The predominantly white and male study population, while highly representative of the veteran population residing in the study sites, may not be generalizable to women or other minority groups (33).

In conclusion, this study suggests that very remote TBI with LOC of at least 30 minutes is an independent risk factor for functionally relevant motor dysfunction—defined as recent falls and impaired gait/posture on exam—among aging military veterans living independently in retirement communities. Thus, with the aging of the veteran and civilian population (34) in combination with the high lifetime prevalence of TBI, increasing numbers of older adults may be living with functionally relevant motor sequelae of prior TBI. Our findings therefore have important implications for the assessment and monitoring of older TBI-exposed adults who may be ideal candidates for targeted fall-prevention strategies.

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