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Medical and environmental risk factors associated with frontotemporal dementia: A case-control study in a veteran population

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Abstract

Background: Compared with other major dementias, very little is known about the medical and environmental risk factors associated with frontotemporal dementia (FTD). In this study, we evaluated medical and environmental disorders associated with FTD in a veteran population.

Methods: The medical records of 845 consecutive veterans who were evaluated for cognitive and/or behavioral complaints at a cognitive disorders clinic in an academic medical center between March 1, 2003, and June 30, 2008, were reviewed and 554 patients received a diagnosis of dementia. Medical disorders and environmental risk factors in 63 patients with behavioral variant of FTD were compared with 491 patients with non-FTD dementias.

Results: The prevalence of traumatic brain injury (TBI) was significantly greater in patients with FTD versus those with non-FTD dementias (12.7% vs 3.5%; $P < .05$). The FTD group also had a lower prevalence of heart disease (19.0% vs 36.7%; $P < .05$) and cerebrovascular diseases (12.7% vs 26.1%; $P < .05$), although the prevalence of vascular risk factors was comparable between FTD and non-FTD dementia groups: hypertension (65.1% vs 68.2%), diabetes (31.7% vs 26.9%), hyperlipidemia (42.9% vs 48.9%), and tobacco use (7.9% vs 8.8%; $P > .05$ for all). In multivariate analysis, the risk for FTD was increased in patients with TBI (OR, 4.4; 95% CI, 1.6–11.8). The risk for FTD was marginally decreased in patients with heart disease (OR, 0.4; 95% CI, 0.3–0.96).

Conclusions: In a clinical sample of veterans, risk of FTD was increased in patients with TBI and marginally decreased in patients with heart disease. Prospective studies are needed to confirm these associations temporally and to identify their underlying mechanisms.

Keywords: Frontotemporal dementia; Veterans; Risk factors; Traumatic brain injury; Heart disease; Cerebrovascular disease

1. Background

Frontotemporal dementia (FTD) is a major cause of early-onset dementia and is the third most common cause of neurodegenerative dementia, accounting for 3% to 6% neuropathologically diagnosed cases of dementia at all ages [1–5]. FTD is characterized by marked behavioral and cognitive dysfunction that results in significantly increased caregiver burden and dependency compared with other common dementia categories, such as Alzheimer's disease (AD) [6].

Compared with other major dementias, the medical and environmental risk factors associated with FTD remain relatively unknown. Genetic factors, however, are known to contribute to FTD and 20% to 40% of patients with FTD have a positive family history [7]. Several genetic mutations have recently been associated with familial FTD. These include mutations in the genes coding for microtubule-associated protein tau, chromatin-modifying protein, valosin-containing protein, trans-activation response DNA-binding protein 43 (TDP-43), and progranulin protein (PGRN) [8–10]. An

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increase in the risk for FTD has been reported with apolipoprotein E genotypes 2 and 4 [11–13] and cystatin C gene (CST 3B) [14]. The long-term depletion of neurotrophic factors, such as cystatin C and PGRN, may be one common theme in frontotemporal lobar degeneration.

The pathophysiological mechanisms underlying the remaining 60% to 80% sporadic cases of FTD are unclear. It is possible that environmental, medical, and hitherto unknown genetic factors contribute to this risk. A study by Rosso et al suggested an increased risk for FTD in patients with head trauma and thyroid disease [15]. However, to our knowledge, these findings have not been replicated.

The primary goal of this study was to investigate medical illnesses and environmental risk factors associated with FTD. We compared these factors between two groups of veterans, those with FTD versus those with non-FTD dementias, presenting to the Cognitive Disorders Clinic of an academic medical center for evaluation of behavioral and/or cognitive complaints.

2. Methods

2.1. Patients

In all, 845 patients were referred to the Cognitive Disorders Clinic at the Michael E. DeBakey Veterans Affairs (VA) Medical Center in Houston, Texas, USA, between March 2003 and June 2008 for cognitive and/or behavioral complaints. Of these, 554 patients were eventually determined to have dementia and were included in the analysis. Those with other diagnoses, such as pseudodementia, were excluded. Among those with dementia, 63 patients were diagnosed with behavioral variant of FTD and the remaining 491 had dementia diagnoses other than FTD.

Patients were evaluated by two behavioral neurologists, who were unaware of the study design. All patients underwent comprehensive clinical and neuropsychological evaluations, laboratory assessments, and brain imaging with computerized tomography or magnetic resonance imaging. Single-photon emission computerized tomography or positron emission tomography was performed as needed to aid in diagnosis.

Dementias were diagnosed using standard criteria [16–20]. FTD was diagnosed using the Neary criteria [17]. The diagnosis of FTD was not considered if brain imaging showed evidence of cerebral contusion or if the symptoms did not progress or improve over follow-up during the study period. AD was diagnosed using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [18], which include deficits in two or more domains of cognition resulting in significant impairment in social or occupational functioning and representing a significant decline from a previous level of functioning. Vascular dementia (VaD) was diagnosed using National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria [19]. Dementia with Lewy bodies (DLB) was diagnosed using criteria suggested by the consortium on DLB [20]. The diagnosis of remaining dementia subtypes was made using Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition [16].

A chart abstraction tool was used for data collection by three medical school graduates (M.W., G.P.P., P.S.), who were blinded to the study design. Data were collected on a number of variables, including age at first visit, gender, neurological diagnoses, medical risk factors for vascular disease (hypertension [HTN], diabetes [DM], hyperlipidemia [HYPL], cardiac and cerebrovascular diseases, current smoking and alcohol use), and diagnoses of cancer, anemia, chronic obstructive pulmonary diseases, renal failure, congestive heart failure, thyroid disease, atrial fibrillation, and self-reported traumatic brain injury (TBI). We inquired about a history of TBI, in the form of head trauma from any cause with alteration of consciousness, from the patient or their loved ones. All instances of such TBI were included.

For a risk factor to be considered valid, it had to precede the onset of dementia. We created two composite variables to simplify this initial exploratory analysis of association of cardiac and cerebrovascular diseases with FTD: (a) *heart disease*, which included diagnoses of coronary artery disease, angina, myocardial infarction, arrhythmia, atrial fibrillation, congestive heart failure, and cardiomyopathy, and (b) *cerebrovascular disease*, which included diagnoses of transient ischemic attack and stroke.

Patients with dementias other than FTD, AD, VaD, and DLB were grouped into a category called "other dementias." This included diagnoses of alcohol-related dementia, Parkinson disease dementia, normal pressure hydrocephalus with dementia, multiple sclerosis-related dementia, human immunodeficiency virus-associated dementia, and dementia not otherwise specified.

This study was approved by the Institutional Review Boards of Baylor College of Medicine, Houston, Texas, USA, and the Michael E. DeBakey Veterans Administration Medical Center Research and Development Committee, Houston, Texas.

2.2. Statistical analyses

Categorical data are presented as frequencies, and continuous data are presented as mean ± standard deviation. The Mann–Whitney *U* test was used to compare means between two groups of continuous, nonparametric variables [21]. The Fisher's exact test was used to test group differences and for bivariate associations [21]. A P value of $<.05$ was considered significant.

Multivariate logistic regression was performed to evaluate associations between FTD and medical/environmental disorders after adjusting for covariates [21]. In the multivariate analyses, the dependent variable was FTD and the independent variables were those associated with FTD in a bivariate analysis with a P value of $<.1$. The association between FTD and TBI or vascular disease can be potentially

confounded by different distributions of risk factors for TBI and vascular diseases between FTD and non-FTD groups. To account for this potential confounder, we calculated propensity scores for vascular disease and TBI individually using logistic regression after entering risk factors associated with these two conditions as covariates [22]. Propensity scores are typically estimated as the predicted probability of belonging to a group (e.g., TBI vs no TBI and vascular disease vs no vascular disease) from a logistic regression, using certain patient characteristics as predictors, that is, those that are likely to predispose the patients to these condition. For vascular disease, this included age, DM, HTN, HYPL, tobacco use, and substance abuse. For TBI, based on previous studies [23–25], this included age, DM, postural hypotension, syncope, alcohol use, substance abuse, cardiac arrhythmia, and seizures. We then used these propensity scores in the multivariate analyses as covariates to further adjust for group differences for determining risk factors associated with FTD [26,27].

We used two models to determine medical risk factors associated with FTD by varying the patient population included in the non-FTD dementia group. In model 1, all patients with dementia were included. The covariates included age, heart disease, cerebrovascular disease, anemia, and propensity scores for vascular diseases and TBI. In model 2, all patients with dementia *except VaD* were included. The covariates for this model were similar to those used in model 1, but excluded cerebrovascular disease owing to lack of association in bivariate analysis.

The efficiency of the multivariate models was evaluated with Hosmer–Lemeshow goodness-of-fit statistics [21]. All statistical analyses were performed using Stata 8.0 (College Station, TX) statistical software [21].

3. Results

3.1. Demographics and sample characteristics

A total of 845 patients were evaluated in the Cognitive Disorders Clinic between 2003 and 2008. Of these, 554 received diagnoses of dementia and were included in the analysis. The remaining patients were excluded because the aim of the study was to evaluate how the risk factors differed between FTD and other dementias (non-FTD dementias).

A diagnosis of behavioral variant of FTD was made in 63 patients (Table 1), whereas 491 patients were diagnosed with non-FTD dementias (Tables 1 and 2) such as AD, VaD, DLB, alcohol-associated dementia, and Parkinson's disease-associated dementia. Among those diagnosed with dementia, the percentages of individual dementia diagnoses were as follows: AD = 52%, VaD = 39.7%, DLB = 8.3%, FTD = 11.4%, and other dementias = 13.9%. Some patients had more than one dementia diagnosis so that the total of individual percentages was greater than 100% and the total number of patients with non-FTD dementias (491) was less than the sum of patients in individual dementia categories. The mean age for patients with FTD was significantly lower than for those with AD ($P < .001$) and VaD ($P < .001$). The mean age of patients with FTD, DLB, and those with other dementias did not differ ($P > .05$).

The distribution of various medical illnesses and environmental risk factors in the study sample is shown in Table 1. The prevalence of HTN, DM, heart disease, cerebrovascular disease, alcohol use, anemia, and TBI differed significantly between dementia categories ($P < .05$). The prevalence of heart disease (19%), cerebrovascular disease (12.7%), and anemia (0%) was lower in patients with FTD compared with those with all non-FTD dementias (heart disease: 30%–46%, cerebrovascular disease: 15%–43%, anemia: 3%–9%). The prevalence of TBI, in contrast, was significantly higher in FTD at 12.7% compared with 2% to 3% in AD, VaD, and DLB (Table 1). The "other dementias" also had a higher prevalence of TBI at 10.4%.

3.2. Medical and environmental risk factors associated with FTD

We then examined the relationship specifically between FTD and medical/environmental factors. In bivariate analyses, we compared FTD (n = 63) with all non-FTD dementia (n = 491) patients (Table 2). FTD was significantly associated with heart disease, cerebrovascular disease, anemia, and TBI ($P < .05$). The prevalence of medical risk factors associated with vascular diseases was comparable with all non-FTD patients ($P > .05$), including those with HTN, DM, HYPL, and tobacco and alcohol use.

3.3. Multivariate logistic regression models

Finally, we tested whether the associations noted in the bivariate analyses persisted after adjusting for covariates in multivariate logistic regression models (Table 3). We used two models: model 1 included all patients with dementia, whereas model 2 included patients with dementia except VaD. Model 2 was included to compare the FTD group with a group of dementia patients who did not have the higher prevalence of cardiovascular risk factors expected in the VaD group.

In model 1, the risk of FTD was marginally reduced in patients with heart disease (OR, 0.4; 95% CI, 0.3–0.96) and was increased 4.4-fold in those with TBI (OR, 4.4; 95% CI, 1.6–11.8). There was no association between FTD and cerebrovascular diseases (OR, 0.5; 95% CI, 0.2–1.1). In model 2, the risk of FTD was borderline lower in patients with heart disease (OR, 0.4; 95% CI, 0.2–0.98) and higher in those with TBI (OR, 3.8; 95% CI, 1.4–10.2).

4. Discussion

We found a distinct medical and environmental profile for FTD versus non-FTD dementias in this sample of veterans. Patients with FTD had a significantly higher prevalence of TBI and, despite similar rates of vascular risk factors, a marginally lower prevalence of heart disease.

Table 1
Demographics and frequency of various risk factors in major dementia categories and the study population

	FTD	AD	VaD	DLB	Other dementias	P*
Number of patients (%)	63 (7.5)	288 (34.1)	220 (26)	46 (5.4)	77 (9.1)	
Age (mean ± SD)	71.3 (11)	77.2 (7.5)	76.6 (7.6)	75.1 (7.8)	68.2 (11)	**<.0001**
Males	62 (98.4)	282 (97.9)	215 (97.7)	46 (100)	75 (97.4)	.7
Hypertension	41 (65.1)	199 (69.1)	175 (78.5)	26 (56.5)	45 (58.4)	**.001**
Hyperlipidemia	27 (42.9)	144 (50)	119 (54.1)	22 (47.8)	31 (40.3)	.2
Diabetes	20 (31.7)	66 (23)	83 (37.7)	10 (21.7)	17 (22.1)	**.003**
Tobacco use	5 (7.9)	22 (7.6)	25 (11.4)	6 (13)	5 (6.5)	.5
Heart disease†	12 (19)	97 (33.7)	100 (45.5)	14 (30.4)	28 (36.4)	**.001**
Cerebrovascular disease‡	8 (12.7)	65 (22.6)	93 (42.3)	10 (21.7)	12 (15.6)	**<.001**
Peripheral vascular disease	2 (3.2)	13 (4.5)	14 (6.4)	0 (0)	4 (5.2)	.5
Renal failure	0 (0)	10 (3.5)	11 (5)	2 (4.3)	1 (1.3)	.3
Alcohol use	8 (12.7)	36 (12.5)	33 (15)	5 (10.9)	21 (27.3)	**.04**
COPD	3 (4.8)	27 (9.4)	27 (12.3)	6 (13)	4 (5.2)	.2
Cancer	7 (11.1)	55 (19.1)	38 (17.3)	4 (8.7)	8 (10.4)	.2
Anemia	0 (0)	25 (8.7)	18 (8.2)	3 (6.5)	3 (3.9)	**.04**
Thyroid disease	5 (7.9)	21 (7.3)	16 (7.3)	4 (8.7)	4 (5.2)	.9
TBI	8 (12.7)	8 (2.8)	6 (2.7)	1 (2.2)	8 (10.4)	**.001**

NOTE. Bold *P* values indicate significance ($P < .05$).

Abbreviations: FTD, frontotemporal dementia; AD, Alzheimer's disease; VaD, vascular dementia; DLB, dementia with Lewy bodies; COPD, chronic obstructive pulmonary disease; TBI, traumatic brain injury.

**P* values for differences across dementia categories of AD, VaD, FTD, DLB, and other dementias.

†"Heart disease" includes diagnoses of coronary artery disease, angina, myocardial infarction, arrhythmia, atrial fibrillation, congestive heart failure, and cardiomyopathy.

‡Cerebrovascular disease includes diagnoses of transient ischemic attack and stroke.

4.1. Frontotemporal dementia and traumatic brain injury

The prevalence of TBI in our sample of patients with FTD was much greater than in patients with non-FTD dementias. In the multivariate analysis, the risk of FTD was 4.4 times greater in individuals with TBI compared with those without TBI. This finding is in agreement to that of Rosso et al who found that head trauma was an independent risk factor for FTD (adjusted OR, 3.3) when compared with age- and gender-matched controls [15].

There may be multiple reasons for this association between TBI and FTD. Because of their locations, the frontal and temporal lobes are more sensitive to head trauma [28,29]. Therefore, TBI may be more likely to produce neurologic disorders of the frontal and temporal lobes.

We previously hypothesized that TBI may lead to an increased risk for FTD through altering brain levels of PGRN [30]. PGRN has been suggested to be involved in neuronal repair and growth. Several groups have shown that FTD

Table 2
Prevalence of heart disease, cerebrovascular disease, and TBI in FTD patients versus non-FTD dementia patients

Variables n (%)	FTD (63)	Non-FTD dementias (491)*
Age (±SD)†	71.3 (11)	75.2 (9)‡
Males	62 (98.4)	482 (98.2)
Medical and environmental factors		
Hypertension	41 (65.1)	335 (68.2)
Hyperlipidemia	27 (42.9)	240 (48.9)
Diabetes	20 (31.7)	132 (26.9)
Tobacco use	5 (7.9)	43 (8.8)
Heart disease	**12 (19)**‡	180 (36.7)
Cerebrovascular disease	**8 (12.7)**‡	128 (26.1)
Peripheral vascular disease	2 (3.2)	21 (4.3)
Renal failure	0 (0)	17 (3.5)
COPD	3 (4.8)	47 (9.6)
Cancer	7 (11.1)	74 (15.1)
Anemia	**0 (0)**‡	34 (7)
Thyroid disease	5 (7.9)	37 (7.5)
Alcohol use	8 (12.7)	74 (15.1)
TBI	**8 (12.7)**‡	17 (3.5)

NOTE. Bold *P* values indicate significant differences.

*Total is less than the total of individual dementia categories owing to overlapping dementia diagnoses.

†Bivariate associations using Mann–Whitney *U* test. The remaining bivariate analyses used Fisher's exact test.

‡$P < .05$ for FTD versus non-FTD dementias group.

Table 3
Adjusted odds ratios and 95% confidence intervals for association of medical and environmental factors with FTD

	Model 1		Model 2	
	All dementias		All dementias except VaD	
Medical and environmental factors	OR (95% CI)	*P*	OR (95% CI)	*P*
Heart disease	0.4 (0.3–0.96)	**.040**	0.4 (0.2–0.98)	**.047**
Cerebrovascular diseases	0.5 (0.2–1.1)	.095	*	
TBI	4.4 (1.6–11.8)	**.003**	3.8 (1.4–10.2)	**.008**

NOTE. Bold values indicate significant differences.

Model 1 included all patients with dementias. The covariates were age, TBI, heart disease, cerebrovascular disease, anemia, and propensity scores for TBI and vascular diseases. Model 2 included all patients with dementias except VaD. The covariates included those in model 1 except cerebrovascular disease.

*Not included in the model owing to lack of association in bivariate analysis.

patients with PGRN gene mutation have insufficient levels of PGRN, which has been postulated to lead to FTD [31,32]. TBI is known to result in activation of microglia in the brain. The activated microglia release elastases, which may cleave PGRN to smaller proinflammatory peptides called granulins, thus causing a deficiency in PGRN levels. This PGRN deficiency state may increase the susceptibility to FTD [30].

TBI could also lead to the clinical presentation of FTD through other plausible mechanisms. Recent neuropathological studies have demonstrated a progressive tauopathy as well as TDP-43 proteinopathy in patients with chronic traumatic encephalopathy [28,33]. It is possible that TBI might initiate a cascade of neuropathological changes that may manifest later as FTD.

Further studies are clearly needed to investigate these possibilities. It is also imperative to study the prevalence of FTD in populations at risk for TBI, such as former military personnel, professional boxers, and race car drivers.

4.2. FTD and cardiovascular diseases

AD and VaD are associated with a higher prevalence of cardiovascular diseases [34]. This is presumably because of a higher prevalence of risk factors for vascular disease. Bivariate analysis in this study showed that the distribution of vascular risk factors was comparable between patients with FTD and those with non-FTD dementias and yet the prevalence of heart disease was lower in the FTD group (Tables 1 and 2). Two factors were likely to confound this association: the younger mean age of the FTD group, and a greater prevalence of heart disease in the patients with VaD. To account for these potential confounding factors, we performed multivariate analysis by excluding patients with VaD, with age as a covariate in addition to other covariates as described previously (Table 3, model 2). After adjusting for these factors, the association between FTD and low rate of heart disease was marginally significant ($P = .047$; Table 3).

The study by Rosso et al shows a comparable prevalence of vascular risk factors in patients with FTD and age-matched controls and a nonsignificant trend ($P = .1$) toward a lower prevalence of myocardial infarction in the FTD group [15]. Another study from Italy found a lower prevalence of vascular risk factors among patients with FTD compared with healthy controls of similar age [35]. Similarly, a study from Oman found a lower prevalence of vascular risk factors and ischemic heart disease in patients with FTD. However, patients with FTD in this study were significantly younger (mean age ± SD, 55.7 ± 7.3) than the AD (69.8 ± 8.5) and VaD (64.8 ± 8.9) patients [36]. A study by Passant et al also found a lower prevalence of HTN, DM, and heart disease among patients with FTD [37]. In this study as well, the mean age of patients with FTD was 63 years compared with78 and 80 years in the patients with AD and VaD, respectively. Thus, it is possible that the lower prevalence of cardiovascular diseases in these studies was because of younger age of the patients with FTD.

It is apparent that the association of FTD and cardiovascular diseases is weak and merits further studies. It becomes very important considering the fact that two vascular risk factors, DM and dyslipidemia, have been recently found to have a "protective" effect in another neurodegenerative disorder, amyotrophic lateral sclerosis [30,38,39].

4.3. Limitations

We advocate a judicious interpretation of this study's results because the adopted methodology has some limitations. The data were obtained by chart review and are thus limited by the information entered in the chart. Because the information on TBI is self-reported, it is subject to recall bias. It is also possible that patients with other dementias where amnesia is more common, for example, AD and DLB, may not have recalled incidences of TBI to the same degree as patients with FTD where amnesia is less common. However, as more objective methods continue to evolve to study TBI, self-reported TBI remains a commonly used method with its inherent limitations [40–43]. Moreover, even in disorders where amnesia is common, it usually applies to anterograde memories more than the retrograde ones used to recall a distant history of TBI.

We also do not have information on the severity, timing, and etiology of TBI, for example, combat exposure, motor vehicle accidents, seizures, and falls in the elderly. Thus, the effect of these factors on the risk of FTD cannot be analyzed in this study. Other potential limitations include a predominance of male patients limiting the generalizability of the results and referral and selection biases in the patient population, given that the patients were selected from a specialty clinic and nondementia patients were excluded from the analysis.

In summary, our study demonstrates a higher prevalence of TBI and a marginally decreased prevalence of heart disease in a sample of veterans with FTD. Prospective studies involving patients with and without TBI who are followed up to determine whether they develop FTD would be needed to assess causal association between TBI and FTD. Such studies should also examine the effects of the etiology of brain injury, severity of brain injury, and duration since TBI at first diagnosis of FTD and should involve more objective imaging methods of assessing brain injury such as diffusion tensor imaging [41]. Furthermore, obtaining neuropathological information in patients with a clinical diagnosis of FTD is likely to give additional information about the neuropathological cascade following TBI. Because we found a marginally significant association between heart disease and FTD, a larger retrospective study using the VA database system can help in further study of this association. If this association is confirmed, a prospective study involving VA or non-VA cohorts may support a causal association.

Based on the emerging literature regarding possible late detrimental neuropathological changes after TBI, it will also be very important to ascertain how the risk of cognitive dysfunction after TBI might be lessened.

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