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Role of brain infarcts in behavioral variant frontotemporal dementia Clinicopathological characterization in the National Alzheimer's Coordinating Center database

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ABSTRACT

Diagnosing behavioral variant frontotemporal dementia (bvFTD) in patients with prior history of stroke or with silent brain infarcts on neuroimaging studies can be challenging. Vascular changes in patients with bvFTD are not unusual, but bvFTD tends to be ruled out in the presence of cerebrovascular disease. We aimed to identify the clinical, cognitive, and risk factor profile of bvFTD with coexistent cerebrovascular disease (V-bvFTD). We compared demographic data, clinical diagnoses, vascular risk factors, functional status, and normalized neuropsychological z-scores between patients with V-bvFTD versus bvFTD without concomitant cerebrovascular disease (NV-bvFTD) from the National Alzheimer's Coordinating Centre database. We included 391 neuropathologically-diagnosed cases of frontotemporal lobe degeneration. We excluded patients that were diagnosed with aphasic variants of frontotemporal dementia before death. Patients with V-bvFTD (n = 62) were older at the time of onset of cognitive decline (71.6 vs. 62.5 years, $p < 0.001$) and death (78.7 vs. 69.6, $p < 0.001$), more likely to be hypertensive (75.8% vs. 45.7%, $p = 0.002$) and to have a history of stroke (21.2% vs. 6.1%, $p = 0.007$) than those with NV-bvFTD (n = 329). V-bvFTD was often underdiagnosed, affected elderly patients, and had a similar cognitive profile as NV-bvFTD despite the presence of brain infarcts. In the whole cohort, we observed enhanced cognitive performance with increasing age quintiles despite larger proportions of cerebrovascular disease pathology, likely meaning that frontotemporal lobe degeneration—related primary neurodegeneration exerts a stronger impact on cognition than cerebrovascular disease. Coexisting cerebrovascular disease should not preclude the diagnosis of bvFTD.

1. Introduction

Frontotemporal lobe degeneration (FTLD) is the term encompassing the underlying pathological findings of frontotemporal dementias (FTD), which share a common process of relatively restricted and rapidly progressive atrophy of the frontal and temporal lobes, displaying a wide array of clinical and neuropathological profiles (Mackenzie et al., 2010; Rademakers et al., 2012). FTD can express as progressive changes in language or behavior. Language is mainly impaired in the aphasic forms, while behavior is

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affected in the behavioral variant. Patients with behavioral variant FTD (bvFTD) show marked impairment of cognitive and behavioral functioning, particularly in social cognition. Other common symptoms of bvFTD are executive dysfunction, inattention, impulsivity, and socially inappropriate behavior (Rascovsky et al., 2011). In the presence of a history of stroke or even when silent brain infarcts are detected on neuroimaging studies, distinguishing between FTD and cerebrovascular behavioral syndromes can be remarkably challenging. Moreover, FTD is often ruled out in the presence of cerebrovascular disease. However, as shown in population-based studies, both conditions can coexist (Prevalence of stroke-United States, 2006–2010, 2012; Ratnavalli et al., 2002). Furthermore, since among subjects aged 60 years or over the prevalence of covert cerebral infarcts is >3-fold higher than that of symptomatic infarcts, the coexistence of FTD, and silent brain infarcts may be even greater than that of FTD and stroke (Price et al., 1997).

Identifying the clinical profile of patients diagnosed with FTLD with coexistent cerebrovascular disease in neuropathology may result in more diagnosed cases and more opportunities to prevent the progression of cerebrovascular disease by treating vascular risk factors. The correct diagnosis bvFTD with coexistent cerebrovascular disease would also ensure the opportunity to provide patients and their families with a more accurate disease prognosis. A better portrayal of these patients would be also beneficial for research purposes.

The problem with most prior FTD studies is that subjects with evident cerebrovascular disease (i.e., brain infarcts on neuroimaging studies) were excluded and, thus, the resulting study populations were possibly subject to selection bias toward the forms of FTD without coexistent cerebrovascular disease. Moreover, most studies were focused on atrophic changes rather than on vascular lesions, which are seldom reported (Davies et al., 2006; Whitwell et al., 2005).

In the present study, we interrogated the National Alzheimer's Coordinating Center (NACC) database and selected patients with neuropathologically confirmed FTLD without premortem clinical diagnosis of aphasic variants of FTD, to compare demographic data, clinical diagnoses before death, vascular risk factors, functional status (clinical dementia rating), and neuropsychological functioning between cases with and without coexistent cerebrovascular disease.

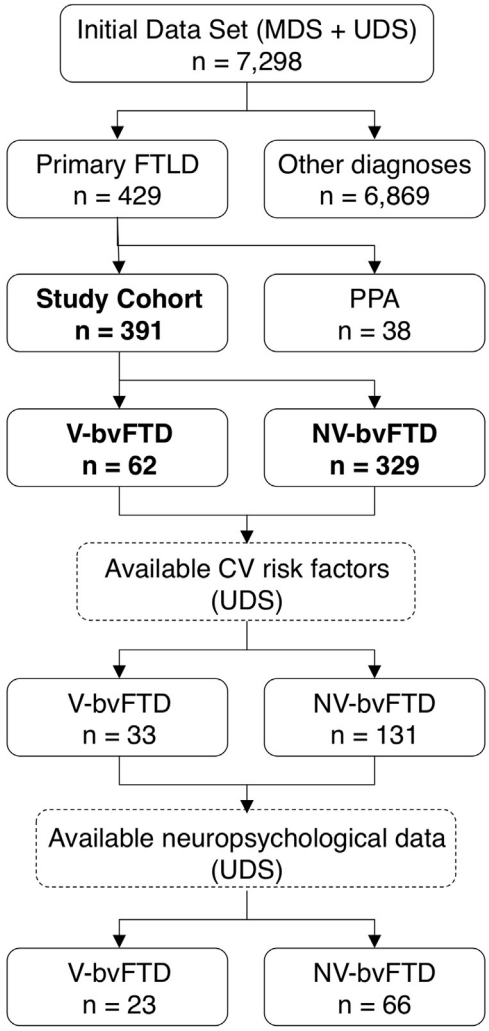

Fig. 1. Description of the study cohort. Abbreviations: CV, cardiovascular; FTLD, frontotemporal lobe degeneration; MDS, minimum data set; NV-bvFTD, behavioral variant frontotemporal dementia without cerebrovascular disease; PPA, primary progressive aphasia; UDS, uniform data set; V-bvFTD, behavioral variant frontotemporal dementia with cerebrovascular disease.

2. Methods

The NACC, established by the National Institute on Aging in 1999 with the aim of enabling collaborative research (U01 AG016976), collects data from 35 past and present National Institute on Aging-funded Alzheimer disease (AD) centers across the USA. For this study, neuropathological data were downloaded from the NACC Neuropathology Data Set, while clinical data from the same cases were obtained from both the NACC Minimum Data Set (MDS) and the NACC Uniform Data Set (UDS) (Beekly et al., 2004, 2007; Weintraub et al., 2009). The MDS was implemented in 1999 and contains information on demographic data, clinical manifestations, clinical diagnoses, and neuropathological diagnoses. The UDS replaced the MDS in 2005, by following still living and active cases in the MDS, recruiting new cases, and recording more comprehensive information (i.e., neurological examination, functional status, neuropsychological assessment, and genetic data). Our analysis was performed using records from the September 2013 freeze of the data sets (August 2013 was the last month included). Further information about the NACC database can be found online (http://www.alz.washington.edu/).

The initial data set comprised 7298 subjects (Fig. 1). For most of the neuropathological diagnoses, 2 categories were available: primary or contributing. Only subjects with primary neuropathological diagnosis of FTLD were selected for this study (n = 429). Among them, we excluded 38 patients with premortem clinical diagnosis of primary progressive aphasia. Therefore, the final cohort comprised 391 patients with pathological diagnosis of primary FTLD but without clinical diagnosis of aphasic variants of FTD. By excluding aphasic variants of FTD, patients with pathology findings of FTLD could most certainly be deemed as either clinical (full expression of dementia) or subclinical (asymptomatic with normal or nearly normal cognition) cases of bvFTD. Clinical diagnoses of the dementia types were done by the referring clinician, based on information obtained through the subject, next of kin, medical records or observation; according to the NACC UDS Coding Guidebook for IVP (version 2.0, February 2008, based on Neary criteria, available at http://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER2/ivpguide.pdf) (Neary et al., 1998). The reason for excluding patients with primary progressive aphasia was that, due to the prominent language disturbances, the clinical diagnosis of aphasic forms is less challenging than the characterization of behavioral variants. Patients were further classified as whether presenting (behavioral variant frontotemporal dementia

Table 1
Comparison of demographic data, vascular risk factors, and comorbidities between V-bvFTD and NV-bvFTD

	V-bvFTD	NV-bvFTD	*p* Value
Demographics			
Age of onset of cognitive decline, mean ± SD (y)	71.6 ± 12.1	62.5 ± 12.0	< 0.001
Age at last assessment, mean ± SD (y)	78.3 ± 11.6	69.6 ± 11.6	< 0.001
Age at death, mean ± SD (y)	78.7 ± 11.3	69.6 ± 11.5	< 0.001
Years of education, % (n)	15.2 ± 2.9	14.8 ± 2.9	0.30
Male sex, % (n)	48.4 (30/62)	58.1 (191/329)	0.16
Vascular risk factors			
Hypertension, % (n)	75.8 (25/33)	45.7 (59/129)	0.002
Diabetes mellitus, % (n)	18.2 (6/33)	8.5 (11/130)	0.10
Hyperlipidemia, % (n)	42.4 (14/33)	40.6 (52/128)	0.85
Smoking, % (n)	45.2 (14/31)	50.0 (64/128)	0.63
Atrial fibrillation, % (n)	12.1 (4/33)	6.9 (9/131)	0.32
Comorbidities			
Coronary artery disease, % (n)	18.2 (6/33)	10.7 (14/131)	0.24
Congestive heart failure, % (n)	3.0 (1/33)	1.5 (2/131)	0.57
Prior TIA, % (n)	8.1 (5/62)	2.3 (3/131)	0.06
Prior stroke, % (n)	21.2 (7/33)	6.1 (8/131)	0.007

Key: NV-bvFTD, diagnosing behavioral variant frontotemporal dementia without concomitant cerebrovascular disease; SD, standard deviation; TIA, transient ischemic attack; V-bvFTD, diagnosing behavioral variant frontotemporal dementia with coexistent cerebrovascular disease.

with cerebrovascular disease [V-bvFTD]) or not (behavioral variant frontotemporal dementia without cerebrovascular disease [NV-bvFTD]) with concomitant vascular lesions on pathological examination. Vascular brain lesions included among findings from the neuropathological examination were large macroscopic infarcts, lacunar macroscopic infarcts, microinfarcts, and intraparenchymal hemorrhage. The criteria used by the neuropathologists to assess the vascular features are described in the Neuropathology Diagnosis Coding Guidebook available at https://www.alz.washington.edu/NONMEMBER/NP/npguide9.pdf. For the purpose of this study, the presence of at least one of any of the abovementioned vascular lesions was enough for considering patients as having V-bvFTD. As a consequence, NV-bvFTD cases were those without any microinfarcts or macroinfarcts. There were no patients with pathological diagnosis of primary cerebrovascular disease.

We analyzed data regarding sex, age at the onset of cognitive decline, age at the last visit, age at death, and years of education. We also used the available information regarding history of hypertension, diabetes mellitus, hyperlipidemia, smoking (>100 cigarettes smoked in a lifetime), history of stroke, transient ischemic attack, atrial fibrillation, congestive heart failure, and coronary artery disease. These clinical variables were only available from the UDS and were obtained by the treating physician (n = 164). They were coded as unknown, absent, recent or active, or remote or inactive. For analytical purposes, active and inactive categories were merged and compared to the absent category. History of stroke was defined as the composite of any of 3 variables comprised in the original data set: stroke (variable #2A), history of stroke (variable #6), and temporal relationship between stroke and onset of cognitive impairment (variable #10). A history of coronary artery disease was defined as present if the patient had a history of "heart attack" (variable #1A), "angioplasty/endarterectomy/stent" (variable #1C), or "cardiac bypass surgery" (variable #1D).

On the basis of underlying neuropathology, FTLD cases were classified as FTLD-tau if they were characterized by tau pathology while those positive for ubiquitin and trans-active-response DNA-binding protein 43 were classified as FTLD-U.

We used the NACC cognitive battery for assessing cognitive status in the last visit before death (Beekly et al., 2007). The battery comprised the following domains and tests: (1) broad cognitive status: Mini-Mental State Examination (Folstein et al., 1975); (2) executive functions: digit span backward (Wechsler Memory Scale-Revised) (Wechsler and Stone, 1987), digit symbol coding (Wechsler Adult Intelligence Scale-Revised) (Wechsler, 1987), and Trail Making Test Part B (Arbuthnott and Frank, 2000); (3) memory: immediate and delayed recall (Story A, Wechsler Memory Scale-Revised) (Wechsler and Stone, 1987); (4) language: animal and vegetable list generation (verbal fluency) (Morris et al., 1989) and Boston naming test (naming) (Kaplan et al., 1983); (5) attention: digit span forward (Wechsler Memory Scale-Revised) (Wechsler and Stone, 1987) and Trail Making Test Part A (Reitan and Wolfson, 1985). The dementia-related functional status was assessed according to the Clinical Dementia Rating (CDR) comprising memory, orientation, judgment, community affairs, home and hobbies, behavior and personality, language, global impairment, and overall mean score (Morris, 1993).

2.1. Statistical analysis

We compared demographics, risk factor profiles, and vascular comorbidities, CDR scores, results of neuropsychological assessments, and neuropathological findings between V-bvFTD and NV-bvFTD cases. All the results of neuropsychological assessments were normalized (z-scores) for age and sex (Shirk et al., 2011). We evaluated the proportion of cerebrovascular disease pathology across increasing age quintiles and we used the Jonckheere-Terpstra test to assess the level of significance of the observed trends. We employed a similar approach to assess trends in cognitive measures across age quintiles. The χ^2 and Fisher exact tests were used to compare categorical variables, and the Mann-Whitney *U* and Student *t* tests were used to compare continuous variables for the non-normally and normally distributed variables. All tests were 2-tailed and a p-value < 0.05 was deemed statistically significant for this analysis. We used IBM SPSS Statistics 20.0 for Macintosh (IBM Corp) for all statistical analyses.

3. Results

Of the 391 cases of neuropathologically confirmed bvFTD, 62 and 329 patients were classified as V-bvFTD and NV-bvFTD, respectively. The comparison of demographic data, vascular risk factors, and comorbidities between V-bvFTD and NV-bvFTD is shown in Table 1. Patients with V-bvFTD were older at the time of onset of cognitive decline (71.6 ± 12.1 vs. 62.5 ± 12.0 years, $p < 0.001$) and at death (78.7 ± 11.3 vs. 69.6 ± 11.5, $p < 0.001$), were more likely to be hypertensive (75.8 vs. 45.7%, $p < 0.001$), and to

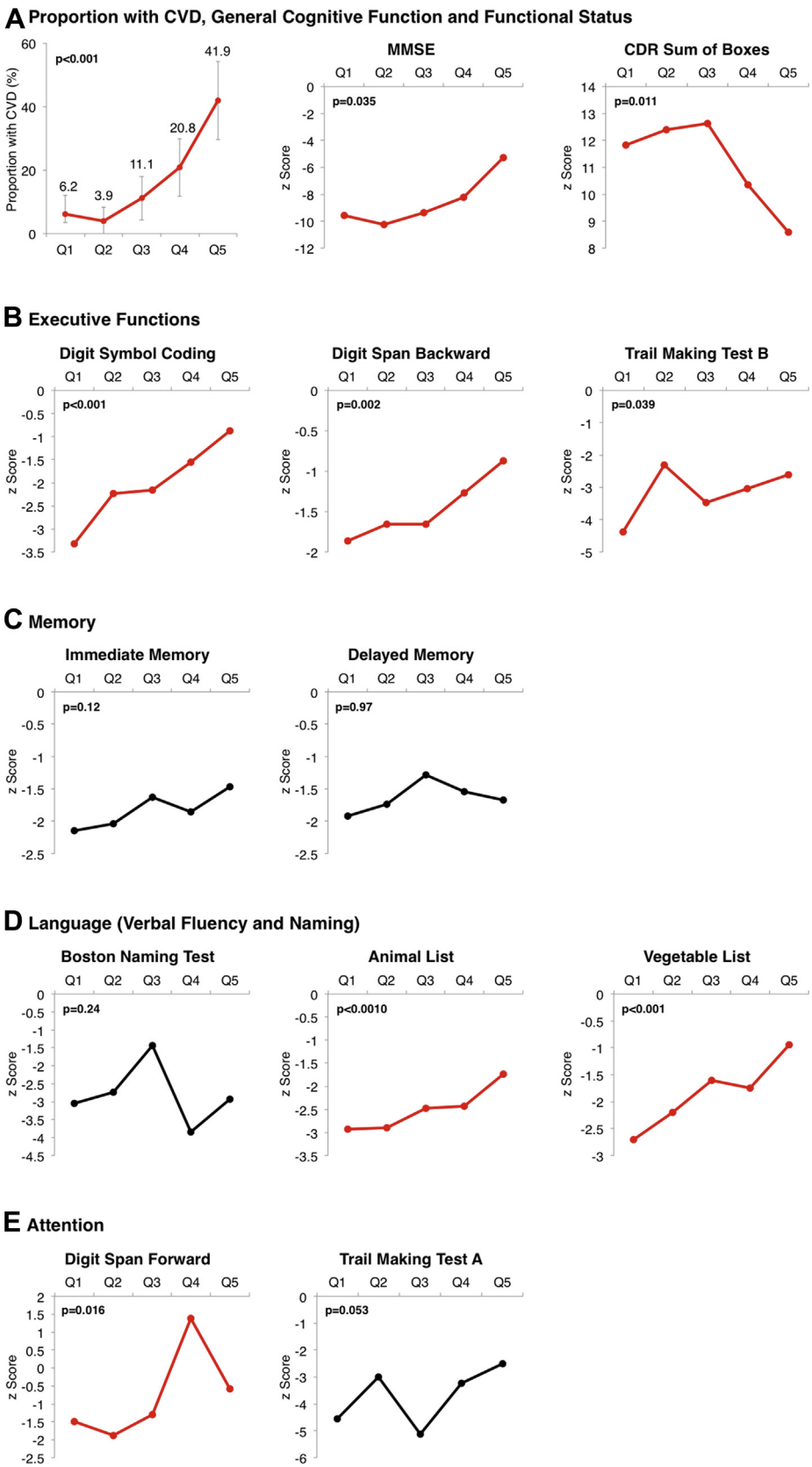

Fig. 2. Proportion with cerebrovascular disease, neuropsychological performance, and functional status across age quintiles. Panel A shows the proportion of cerebrovascular disease pathology (e.g., large infarcts, lacunes, or microinfarcts across age quintiles, general cognitive performance (MMSE), and functional status (CDR sum of boxes) across age quintiles. Panels B–E show the trends for tests of executive functioning, memory, language, and attention, respectively. *p* Values were obtained by using the Jonckheere-Terpstra test for trends. Red and black lines represent significant ($p < 0.05$) and nonsignificant ($p \geq 0.05$) trends, respectively. Abbreviations: CDR, Clinical Dementia Rating; Q, Quintile; MMSE, Mini-Mental State Examination. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Comparison of neuropsychological performance and functional status of V-bvFTD and NV-bvFTD

	V-bvFTD	NV-bvFTD	*p* Value
General cognitive function			
Mini-Mental State Examination, mean ± SD z-score	−8.31 ± 8.0	−8.76 ± 7.19	0.64
Executive functions			
Digit symbol coding, mean ± SD z-score	−1.62 ± 1.64	−1.96 ± 1.47	0.48
Digit span backward (trials), mean ± SD z-score	−1.23 ± 1.33	−1.49 ± 1.08	0.37
Trail Making Test-B, mean ± SD z-score	−1.82 ± 1.87	−3.33 ± 1.84	0.022
Memory			
Immediate memory, mean ± SD z-score	−1.60 ± 1.54	−1.93 ± 1.29	0.37
Delayed memory, mean ± SD z-score	−1.74 ± 1.48	−1.66 ± 1.17	0.84
Language (verbal fluency and naming)			
Boston, mean ± SD z-score	−3.11 ± 3.34	−2.75 ± 3.11	0.68
Animal list, mean ± SD z-score	−1.96 ± 1.11	−2.56 ± 0.94	0.005
Vegetable list, mean ± SD z-score	−1.45 ± 1.31	−1.85 ± 1.14	0.20
Attention			
Digit span forward (trials), mean ± SD z-score	−0.72 ± 1.67	−1.44 ± 1.36	0.054
Trail Making Test-A, mean ± SD z-score	−2.98 ± 2.85	−3.58 ± 3.11	0.51
Clinical Dementia Rating			
Memory, mean ± SD	0.86 ± 1.17	0.63 ± 1.06	0.13
Orientation, mean ± SD	0.83 ± 1.20	0.62 ± 1.08	0.20
Judgment, mean ± SD	0.89 ± 1.20	0.80 ± 1.19	0.58
Community affairs, mean ± SD	0.79 ± 1.15	0.84 ± 1.19	0.78
Home and hobbies, mean ± SD	0.94 ± 1.26	0.85 ± 1.24	0.62
Personal care, mean ± SD	0.78 ± 1.24	0.80 ± 1.21	0.89
Behavior and personality, mean ± SD	0.40 ± 0.94	0.34 ± 0.84	0.63
Language, mean ± SD	0.30 ± 0.84	0.35 ± 0.88	0.68
Global impairment, mean ± SD	0.84 ± 1.15	0.76 ± 1.17	0.63
Sum of boxes, mean ± SD	9.8 ± 6.5	11.6 ± 5.4	0.13

Key: NV-bvFTD, diagnosing behavioral variant frontotemporal dementia without concomitant cerebrovascular disease; SD, standard deviation; V-bvFTD, diagnosing behavioral variant frontotemporal dementia with coexistent cerebrovascular disease.

Table 3
Comparison of premortem clinical diagnoses and neuropathology between V-bvFTD and NV-bvFTD

	V-bvFTD	NV-bvFTD	*p* Value
Clinical diagnosis			
Normal cognition, % (n)	0.0 (0/62)	0.8 (9/329)	0.19
Non-aphasic frontotemporal dementia, % (n)	45.2 (28/62)	40.4 (133/329)	0.49
Cerebrovascular disease, % (n)	3.2 (2/62)	2.4 (8/329)	0.72
Probable or possible Alzheimer disease, % (n)	27.4 (17/62)	22.2 (73/329)	0.37
Dementia with Lewy bodies, % (n)	8.1 (5/62)	1.5 (5/329)	0.003
Progressive supranuclear palsy, % (n)	9.7 (6/62)	7.5 (25/329)	0.58
Parkinson's disease, % (n)	0.0 (0/62)	1.5 (5/329)	0.33
Corticobasal degeneration, % (n)	11.3 (7/62)	9.1 (30/329)	0.59
Dementia secondary other causes, % (n)	16.1 (10/62)	16.4 (54/329)	0.95
Dementia of undetermined cause, % (n)	4.8 (3/62)	1.2 (4/329)	0.048
Neuropathology			
FTLD groups			
FTLD-tau, % (n)	85.2 (46/54)	79.9 (222/278)	0.36
FTLD-U, % (n)	14.8 (8/54)	20.1 (56/278)	
FTLD types			
Undetermined FTLD-tau, % (n)	4.8 (3/62)	7.9 (26/329)	0.40
FTLD-U, % (n)	12.9 (8/62)	17.0 (56/329)	0.42
Nonspecified FTLD, % (n)	12.9 (8/62)	15.5 (51/329)	0.60
Corticobasal degeneration, % (n)	8.1 (5/62)	13.4 (44/329)	0.25
Pick, % (n)	12.9 (8/62)	15.2 (50/329)	0.64
Progressive supranuclear palsy, % (n)	19.4 (12/62)	20.1 (66/329)	0.90
Primary age-related tauopathy−AGD, % (n)	29.0 (18/62)	10.9 (36/329)	<0.001
Neurofibrillary tangles and amyloid deposition			
Braak & Braak V and VI, % (n)	6.7 (4/60)	3.2 (10/308)	0.21
CERAD C, % (n)	5.0 (3/60)	2.7 (8/298)	0.34
Vascular findings			
Large infarcts, % (n)	29.0 (18/62)	0.0 (0/322)	<0.001
Lacunar infarcts, % (n)	59.7 (37/62)	0.0 (0/322)	<0.001
Microinfarcts, % (n)	40.3 (25/62)	0.0 (0/322)	<0.001
Other neuropathological findings			
Hippocampal sclerosis, % (n)	8.5 (5/59)	9.4 (30/318)	0.82
Amyloid angiopathy, % (n)	10.0 (6/60)	6.0 (19/317)	0.25

Diagnoses may overlap since the addition of the frequency of different diagnoses does not equal 100%.
Key: AGD, argyrophilic grain disease; CERAD, Consortium to Establish a Registry for Alzheimer's disease; FTLD, frontotemporal lobe degeneration; NV-bvFTD, behavioral variant frontotemporal dementia without concomitant cerebrovascular disease; V-bvFTD, behavioral variant frontotemporal dementia with coexistent cerebrovascular disease.

have a history of stroke (21.2% vs. 6.1%, $p = 0.004$) compared to those with NV-bvFTD. As expected, large infarcts (29.0% vs. 0.0%, $p < 0.001$), lacunar infarcts (59.7% vs. 0.0%, $p < 0.001$), and microinfarcts (40.3% vs. 0.0%, $p < 0.001$) were more frequent among the V-bvFTD group than among NV-bvFTD subjects. The proportion of patients with cerebrovascular disease pathology increased with each age quintile ($p < 0.001$) (Fig. 2A). FTLD-tau pathology predominated over FTLD-U in both V-bvFTD (85.2%) and NV-bvFTD (79.9%), without differences between groups ($p = 0.36$).

The last cognitive assessment before death showed that V-bvFTD patients had better performances in only 1 test involving executive functioning (normalized Trail Making Test B −1.82 ± 1.87 vs. −3.33 ± 1.84, $p = 0.022$) and 1 test assessing naming (animal list −1.96 ± 1.11 vs. −2.56 ± 0.94, $p = 0.005$) than NV-bvFTD subjects (Table 2). There were no differences in the sum of boxes of the CDR or on any of its items between the 2 groups (Table 2). Interestingly, almost all measures of cognitive function and functional status improved across increasing age quintiles (Fig. 2A–E).

Table 3 shows the clinical diagnoses given to the patients during follow-up. Some cases received multiple diagnoses and thus, the addition of the frequency of different diagnoses does not equal 100%. Dementias with Lewy bodies and of undetermined cause were more frequently diagnosed among patients with cerebrovascular disease than among those without. There were no other major significant differences in regards to clinical diagnoses between groups.

Regarding FTLD types, there were no differences between V-bvFTD and NV-bvFTD, with the exception of primary age-related tauopathy-argyrophilic grain disease (PART-AGD), which was most frequently diagnosed among patients with V-bvFTD (29.0% vs. 10.9%, $p < 0.001$) (Table 3).

4. Discussion

Patients with V-bvFTD represent a significant diagnostic challenge in clinical practice. As some neuropsychological findings (e.g., inattention and executive dysfunction) can be explained by cerebrovascular disease, diagnosing bvFTD in subjects with a prior stroke or with brain infarcts on neuroimaging studies may be arduous. Moreover, patients with evident cerebrovascular disease are excluded from FTD studies, which can potentially lead to bias when characterizing the clinical, pathological, and prognostic profile of FTD in the medical literature (Davies et al., 2006; Whitwell et al., 2005). These knowledge gaps could ultimately result in patients being misdiagnosed. Identifying the clinicopathological profile of V-bvFTD may likely result in more accurate diagnoses and

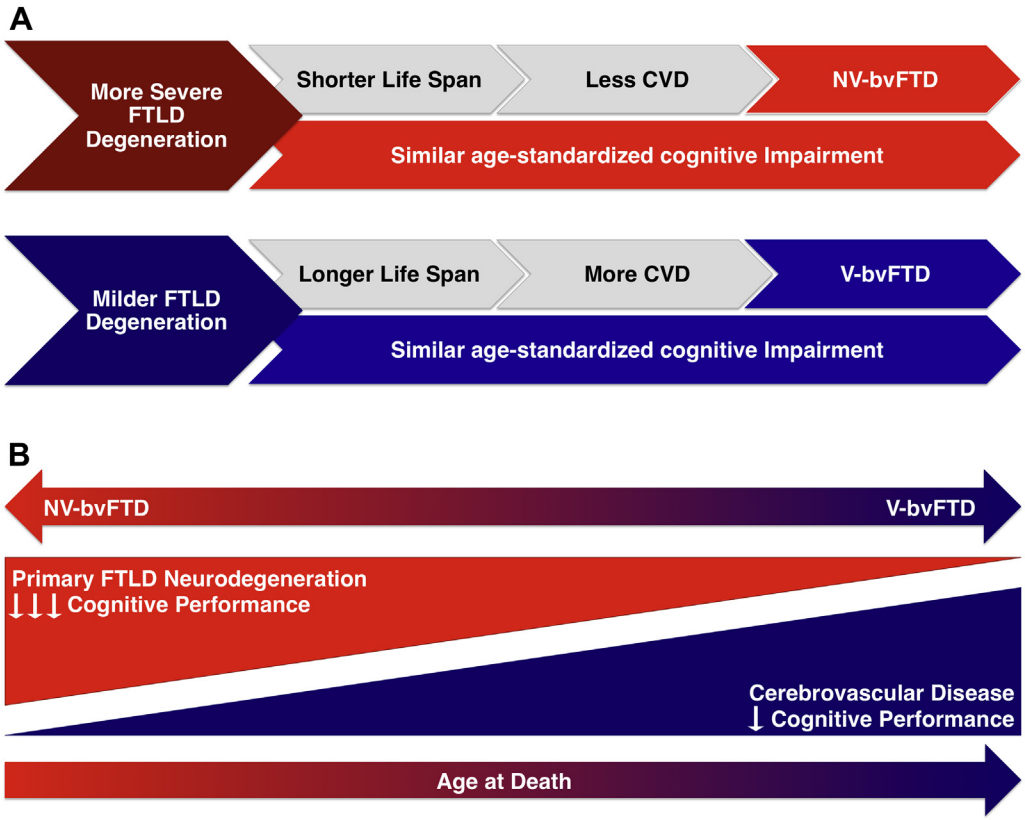

Fig. 3. Hypothetical model explaining the relationship between FTLD primary neurodegeneration, cerebrovascular disease, and cognitive impairment. The hypothetical model shows that milder FTLD neurodegenerative processes result in a longer life span, ultimately leading to a greater exposure to vascular risk factors and cerebrovascular disease (A). According to this model, V-bvFTD and NV-bvFTD represent extreme phenotypes of the variety of possible combinations of degrees of primary FLTD neurodegenerative processes and proportions of cerebrovascular disease pathology (B). Primary FTLD neurodegenerative processes may have a greater impact on cognitive performance than cerebrovascular disease. Abbreviations: CVD, cerebrovascular disease; FTLD, frontotemporal lobe degeneration; NV-bvFTD, behavioral variant frontotemporal dementia without cerebrovascular disease; V-bvFTD, behavioral variant frontotemporal dementia with cerebrovascular disease.

better treatment opportunities. In the present, anatomopathological study comprising 391 cases from the NACC, we aimed to characterize the demographic and vascular risk factor profiles, functional status, and neuropsychological functioning of neuropathologically confirmed cases of V-bvFTD.

Patients with V-bvFTD were older at the time of onset of cognitive decline and at death, were more likely to be hypertensive, and over 3-fold more prone to have a history of stroke than those with NV-bvFTD. There were almost no differences regarding the neuropsychological and functional status of both groups. Cognition and functional status improved with increasing age quintiles in the whole cohort. The clinical diagnosis of bvFTD was made twice as frequently among patients with NV-bvFTD as among those with V-bvFTD. Surprisingly, probable or possible AD was diagnosed twice as frequent in V-bvFTD subjects than in those with NV-bvFTD. Moreover, half of V-bvFTD cases were clinically diagnosed with AD. There were no differences in the frequency of tau pathology between both forms of bvFTD. PART-AGD was 3 times more frequent in the V-bvFTD group than among NV-bvFTD cases. As expected, all types of infarcts were more prevalent among the V-bvFTD group and the proportion of patients with cerebrovascular disease escalated across increasing age quintiles.

Patients with V-bvFTD were, on average, 9 years older at the onset of cognitive decline and at death than those with NV-bvFTD. Similar findings were described for other neurodegenerative diseases such as AD and a-synucleinopathy (Toledo et al., 2013). This finding is likely explained by more severe and rapid neurodegenerative processes occurring in patients with pure NV-bvFTD. A younger onset may be a marker of more aggressive neurodegeneration. We were not able to test the association between less severe neurodegeneration and more frequent cerebrovascular disease because there were no available measures of the burden of disease pathology for confirmed cases of bvFTD. However, we were able to show that despite larger proportions of cerebrovascular disease pathology across increasing age quintiles, cognitive performance was better with older age, meaning that more severe primary FTLD neurodegenerative processes likely explained the worse cognitive functioning of younger patients. Similarly, an association between greater presence of cerebrovascular disease pathology and lower neurofibrillary tangle Braak stages was shown in AD cases from the NACC and from other cohorts (Petrovitch et al., 2005; Toledo et al., 2013). Furthermore, patients with earlier onset FTLD show more severe atrophy of the frontal and temporal lobes than elderly FTLD patients (Baborie et al., 2012). Accordingly, the PART-AGD, a subtype of FTLD affecting very old individuals, usually showing milder degrees of neurodegeneration, was more frequent in patients with V-bvFTD (29.0%) compared to those with NV-bvFTD (10.9%) (Crary et al., 2014; Jellinger and Attems, 2007). We therefore hypothesize that patients who present as V-bvFTD exhibit a slower neurodegenerative disease process, which allows them to live longer. Furthermore, the longer life span of V-bvFTD relative to NV-bvFTD patients may make them more prone to developing hypertension and other vascular risk factors which subsequently lead to cerebrovascular lesions. Cerebrovascular disease pathology in FTLD patients might thus

partially lower the threshold for dementia but not significantly enough to equal the degree of cognitive dysfunction caused by degeneration itself (Jellinger, 2010).

The improvement in cognitive tasks with increasing age may be also explained by selection bias. By dying earlier, NV-bvFTD patients, who harbor the more toxic form of the disease, may have contributed less to the overall changes in scores across increasing quintiles.

The neuropsychological findings of bvFTD subjects in our study are consistent with the classical cognitive profile of patients with bvFTD, typically including impaired attention and executive functions (Garcin et al., 2009). Age- and sex-normalized cognitive performance and functional status of patients with V-bvFTD and NV-bvFTD were similar. We, therefore, propose a hypothetical model capable of explaining the present findings in which V-bvFTD and NV-bvFTD represent extreme phenotypes of the various possible combinations of degrees of primary frontotemporal lobar degeneration neurodegenerative processes and proportions of cerebrovascular disease pathology (Fig. 3). Because of this, the highest proportion of cerebrovascular disease pathology in the V-bvFTD group combined with likely lower frequencies of severe neurodegeneration, may have resulted in a similar extent of age-normalized cognitive dysfunction when compared NV-bvFTD patients who had no cerebrovascular disease and probably the most severe neurodegenerative changes (Baborie et al., 2011; Chui et al., 2006; De Reuck et al., 2012; Esiri et al., 1999; Norton et al., 2014; Toledo et al., 2013).

There are some limitations to the present study that should be taken into consideration. First, although presenting a large size sample, the proportion of available neuropsychological assessments and clinical diagnoses from the NACC database were limited. Also, the battery for neuropsychological testing used in the NACC is not comprehensive, although it covers all the clinically significant cognitive domains. The lack of neuropsychological assessments for some patients could have been the consequence of selection bias (e.g., patients with more severe dementia not being assessed at later stages of the disease) and may hence not be representative of the overall cohort. Second, none of the used cognitive measures constitute a specific tool for evaluating patients with bvFTD and more specific tools could give more information related to their cognition. For instance, recently developed measures such as the Frontotemporal rating scale could have helped to better characterize the clinical profile of the participants (Hornberger and Hodges, 2010). Despite the limitations regarding the cognitive and functional assessments, the scope of our study was broader, comprising demographic data, vascular risk factors profiles, clinical diagnoses, and neuropathological examinations. Finally, we did not have information related to the localization of brain infarcts and the genetic status of bvFTD patients, which could have enriched the analysis and the interpretation of our results.

In conclusion, in our study of 391 neuropathologically confirmed cases of bvFTD from the NACC, we assessed the role of cerebrovascular disease in bvFTD. Our findings suggest that V-bvFTD is characterized by less severe neurodegeneration, thus enabling the additive effect of vascular risk factors to express later in life. Accordingly, older age, a prominent vascular risk factor profile, a history of stroke or transient ischemic attack, and the presence of brain infarcts on neuroimaging studies, rather than precluding the clinical diagnosis of FTD should prompt the initiation of the most intense vascular prevention strategy with the aim of reducing the extent of neuropsychological and functional impairment of patients with this apparently distinctive entity.

Disclosure statement

Dr. Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is co-inventor and he received revenue from the sale of Avid to Eli Lily as co-inventor on imaging related patents submitted by the University of Pennsylvania. He receives research support from the NIH, GSK, Janssen, and several nonprofits. Walter A. Kukull is funded primarily by an NIH grant U01AG016976 (NACC). The remaining authors disclose no conflicts.

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