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Are we comparing frontotemporal dementia and Alzheimer disease patients with the right measures?

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Abstract

Background—Clinical research studies of behavioral variant frontotemporal dementia (bvFTD) often use Alzheimer disease (AD) as a comparison group for control of dementia variables, using tests of cognitive function to match the groups. These two dementia syndromes, however, are very different in clinical manifestations, and the comparable severity of these dementias may not be reflected by commonly used cognitive scales such as the Mini-Mental State Examination (MMSE).

Methods—We evaluated different measures of dementia severity and symptoms among 20 people with bvFTD compared to 24 with early-onset AD.

Results—Despite similar ages, disease-duration, education, and cognitive performance on two tests of cognitive function, the MMSE and the Montreal Cognitive Assessment (MoCA), the bvFTD participants, compared to the AD participants, were significantly more impaired on other measures of disease severity, including function (Functional Assessment Questionnaire (FAQ)), neuropsychiatric symptoms (Neuropsychiatric Inventory (NPI)), and global dementia stage (Clinical Dementia Rating Scales (CDRs)). However, when we adjusted for the frontotemporal

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lobar degeneration-CDR (FTLD-CDR) in the analyses, the two dementia groups were comparable across all measures despite significant differences on the cognitive scales.

Conclusion—We found tests of cognitive functions (MMSE and MoCA) to be insufficient measures for ensuring comparability between bvFTD and AD groups. In clinical studies, the FTLD-CDR, which includes additional language and behavior items, may be a better overall way to match bvFTD and AD groups on dementia severity.

Keywords

Alzheimer disease; behavioral and psychological symptoms of dementia; frontotemporal dementia; neuropsychiatric symptoms; research design and methodology

Introduction

Clinical research studies of bvFTD often use participants with AD, the prototypical dementia, as a comparison group, generally relying on tests of cognitive function to match the groups. The use of an AD control group is intended for control for those variables common to dementias, such as the effects of having multiple cognitive impairments, a decline from a prior higher level of performance, evidence of daily functional impairment, and the psychosocial consequences of these conditions. These two dementia syndromes, however, are very different in clinical manifestations. People with bvFTD are most markedly impaired in behavior, personality, and in executive functions, in contrast to people with AD who are generally most impaired in memory, language, and visuospatial functions (Rascovsky *et al.*, 2011). Therefore, the common practice of using cognitive scales to compare these different dementias is problematic, because the most affected domains differ, and the severity of the illness is not fully captured by cognitive assessment alone. For example, since the MMSE emphasizes testing of orientation and language, and in smaller part memory, persons affected by AD would be expected to perform worse than those with bvFTD at a similar stage of disease.

Despite these limitations, bvFTD and AD participants in research studies are commonly matched by MMSE or other cognitive scale scores (Gregory *et al.*, 2002; Kertesz *et al.*, 2003; Rascovsky *et al.*, 2005), as well as age, years of education, and disease duration: As an example, Gregory *et al.* (2002) compared bvFTD and AD participants on their performance on theory of mind tests, and matched the groups by MMSE as a marker for dementia severity.

When matching by MMSE, people with bvFTD may still demonstrate more global impairment than their matched AD controls. For example, Rosen *et al.* (2004) reported that dementia stage, as measured by the CDRs sum of boxes, was significantly worse among bvFTD participants who had been matched to AD participants by age and MMSE score. Investigators have introduced a new form of the CDR, the FTLD-CDR Scale (Knopman *et al.*, 2008; 2011), which has additional items for behavior and language, and which may prove a better instrument for matching dementia groups than the typical cognitive scales.

We aimed to evaluate bvFTD and AD participants on measures of cognition, function, neuropsychiatric symptoms, and dementia stage, and the value of the extended FTLD-CDR for comparing these participants. We hypothesized that the two dementia groups would be dissimilar across these measures, but if the groups were comparable by FTLD-CDR scores, then they would then have similar functional and neuropsychiatric symptom severity.

Methods

Participants

Patients from a university-based clinic specializing in early-onset dementias were consecutively enrolled in a single-center prospective trial of bvFTD and AD, a larger study from which the selected measures were analyzed. Since the clinic specialized in early-onset dementias, the participants with AD all had early-onset AD (eoAD) with symptom onset prior to 65 years old, except one person with onset at 68 years old. All bvFTD participants met International Consensus Criteria (Rascovsky *et al.*, 2011) and AD participants were diagnosed by McKhann *et al.*, criteria (McKhann *et al.*, 1984). All participants were evaluated by a behavioral neurologist (M.F.M.) and underwent a battery of tests. Cognitive measurements included the MMSE (Folstein *et al.*, 1983) and the MoCA, which has a greater emphasis on executive function than the MMSE (Freitas *et al.*, 2012). Both tests have scores that range from 0 to 30, with lower scores representing greater impairment.

As criteria for dementia severity, this study evaluated common dementia measures of function, behavior, and global dementia stage. Functional status was measured by the FAQ (Pfeffer *et al.*, 1982) total score (range 0–30, with higher scores representing greater impairment). Behavior and psychological symptoms were assessed with the NPI (Cummings, 1997), using the sum of symptoms present (scores range from 0–12, with higher scores representing greater impairment). Global dementia stage was assessed with the original CDR sum of boxes, which measures performance in memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, and with its newer FTLD-CDR sum of boxes modification (Knopman *et al.*, 2011), which adds items for behavior and language. Clinicians score each of the eight categories, based on an informant's report of the participant's abilities, as asymptomatic (0 points), questionable (0.5), mild (1), moderate (2), or severe (3). The summed score ranges from 0–24, with higher scores representing greater impairment. Participants with a standard CDR sum of boxes score less than 1, indicative of questionable or no impairment, were excluded. All participants or their authorized representative provided written consent and the study was approved by our Institutional Review Board.

Data Analysis

Statistical analyses were performed using SAS 9.3 for Windows and $p < 0.05$ was considered to be statistically significant. Demographic variables were compared between bvFTD and eoAD participants using χ^2 tests for categorical variables and two-group t -tests for continuous variables. Normality was examined, and non-normally distributed measures were log-transformed. Linear regressions with a group indicator (bvFTD vs. eoAD) were used to compare mean scores for the MMSE, MoCA, NPI, FAQ, and FTLD-CDR between

the two participant groups (unadjusted analyses). We added an overall dementia severity (FTLD-CDR) to the unadjusted regression models to evaluate if the group differences in the measures of interest remained (adjusted analyses).

Results

We identified 20 bvFTD and 24 eoAD participants evaluated between April 2010 and June 2014. Mean age, years of education, and disease duration were comparable between groups (Table 1). Although the cognitive scales (MMSE and MoCA scores) were similar between bvFTD and eoAD groups, the participants significantly differed on the other dementia severity measures that assessed neuropsychiatric symptoms (NPI), functional status (FAQ), and dementia stage (CDR and FTLD-CDR).

The bvFTD participants had significantly worse neuropsychiatric scores on the NPI compared to eoAD participants [difference = 2.86, 95%CI: 1.37, 4.35; $p < 0.001$] (Table 1). Greater functional impairment as measured on the FAQ was also seen in the bvFTD participants compared to eoAD [difference = 6.46, 95%CI: 2.35, 10.56; $p = 0.003$].

The bvFTD participants had significantly worse overall dementia severity as assessed by the FTLD-CDR [difference = 3.95, 95% CI: 2.67, 5.23; $p < 0.001$] (Table 2). On the individual items, the orientation and language items were found to be similar between groups; however, all other items were significantly worse in bvFTD, except for memory, which was significantly worse in eoAD.

In the adjusted analyses, controlling for FTLD-CDR, the NPI and FAQ scores were no longer significantly different between the bvFTD and eoAD groups. However, both the mean MMSE score and mean MoCA score were greater in the bvFTD group compared to the eoAD group ($p < 0.001$ and $p < 0.05$, respectively). Since the distribution of the MMSE score did not pass the normality test, the same regression analyses with the log-transformed MMSE were performed and the results were found to be similar.

Discussion

In clinical research studies, it is important to compare participants with different types of dementia with a measure that can control for the shared or common aspects of having a dementia; this is particularly true in bvFTD research. Executive function and behavior are most affected in bvFTD participants, whereas in AD, the “prototypical dementia” usually used as a comparison group, memory is primarily affected, along with visuospatial function and language. Investigators commonly use the MMSE and other global tests of cognitive function to match bvFTD and AD participants; however, this cognitive assessment is skewed to AD and is not comprehensive enough to account for the salient aspects of bvFTD. This study found that tests of cognitive function are insufficient for matching bvFTD and AD participants, as reflected in their continued differences on measures of behavior, function, and dementia stage, and suggests that the FTLD-CDR is a better measure for matching these two dementias.

We found that when bvFTD and eoAD participants with similar disease durations have similar cognitive scores on the MMSE and the MoCA, the bvFTD participants have more disturbances in neuropsychiatric symptoms and function, and are more advanced in dementia stage. Our results are in-line with previous studies that have compared bvFTD and eoAD participants. Rosen *et al.* (2004) used the original 6-item CDR and similarly reports that people with bvFTD are worse than those with eoAD in the categories of judgment and problem solving, community affairs, home and hobbies, and personal care, despite comparable MMSE scores. Using the expanded FTLN-CDR, we find that the category of behavior, compositment, and personality is also more impaired among bvFTD participants compared to those with eoAD. Lima *et al.* (2013) further report that bvFTD participants have significantly worse function compared to the eoAD participants, as measured by the FAQ. In their study, they matched the dementia groups by the original CDR, and so it is not known if matching by the FTLN-CDR could have created more equivalent groups, as we suggest.

When we controlled for dementia stage with the FTLN-CDR, the dementia groups became comparable on neuropsychiatric symptoms and functional status; however, significantly better cognitive test scores for the bvFTD participants emerged after controlling for FTLN-CDR. This finding illustrates the fact that tests of cognitive function, particularly the MMSE, with its emphasis on orientation (10/30 items), language (8/30), and in smaller part memory (3/30), are not a good measure for evaluating the stage of dementia among people with bvFTD. People with AD would be expected to be worse than people with bvFTD of comparable dementia stage since the cognitive domains assessed by the MMSE are those most prominently affected in AD. Even the MoCA, with its added executive function items, emerged as significantly worse among those with AD compared to those with bvFTD.

Our study has potential limitations. The participants were recruited from a specialty clinic at a tertiary care hospital, and may not be representative of the general population of people living with dementia. We also evaluated only people with bvFTD and eoAD, and cannot generalize these findings to the larger population of those with diseases on the frontotemporal degeneration spectrum or late-onset AD. In addition, many other scales exist for testing cognition (Cullen *et al.*, 2007), functional status (Desai *et al.*, 2004), and neuropsychiatric symptoms (Apostolova and Cummings, 2008) in people with dementia, in addition to those used in this study, and we do not know how the FTLN-CDR would have fared in the context of these other measures.

Currently, there is no optimal measure for comparing people with different dementias. We found two cognitive scales, the MMSE and the MoCA, to be insufficient measures for ensuring comparability between bvFTD and AD groups, even at similar disease durations. The FTLN-CDR, which was developed, in part, for this purpose, may be better than cognitive scales for matching participants on global dementia stage, and should be considered for use in research studies. Future studies are warranted to create an even more comprehensive and accurate scale that can allow for comparisons between various types of dementia.

References

- Apostolova LG, Cummings JL. Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. *Dementia and Geriatric Cognitive Disorders*. 2008; 25:115–126. DOI: 10.1159/000112509 [PubMed: 18087152]
- Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. *Journal of Neurology, Neurosurgery and Psychiatry*. 2007; 78:790–799. DOI: 10.1136/jnnp.2006.095414
- Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. *Neurology*. 1997; 48:S10–16. DOI: 10.1212/WNL.48.5_Suppl_6.10S [PubMed: 9153155]
- Desai AK, Grossberg GT, Sheth DN. Activities of daily living in patients with dementia: clinical relevance, methods of assessment and effects of treatment. *CNS Drugs*. 2004; 18:853–875. [PubMed: 15521790]
- Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. *Archives of General Psychiatry*. 1983; 40:812. doi: 10.1001/archpsyc.1983.01790060110016 [PubMed: 6860082]
- Freitas S, Simoes MR, Alves L, Duro D, Santana I. Montreal cognitive assessment (MoCA): validation study for frontotemporal dementia. *Journal of Geriatric Psychiatry and Neurology*. 2012; 25:146–154. DOI: 10.1177/0891988712455235 [PubMed: 22859702]
- Gregory C, et al. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain : A Journal of Neurology*. 2002; 125:752–764. DOI: 10.1093/brain/awf079 [PubMed: 11912109]
- Kertesz A, Davidson W, McCabe P, Munoz D. Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia. *Alzheimer Disease and Associated Disorders*. 2003; 17:223–229. DOI: 10.1097/00002093-200310000-00005 [PubMed: 14657786]
- Knopman DS, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain : A Journal of Neurology*. 2008; 131:2957–2968. DOI: 10.1093/brain/awn234 [PubMed: 18829698]
- Knopman DS, Weintraub S, Pankratz VS. Language and behavior domains enhance the value of the clinical dementia rating scale. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. 2011; 7:293–299. DOI: 10.1016/j.jalz.2010.12.006
- Lima-Silva TB, et al. Functional profile of patients with behavioral variant frontotemporal dementia (bvFTD) compared to patients with Alzheimer's disease and normal controls. *Dementia & Neuropsychologia*. 2013; 7:96–103.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology*. 1984; 34:939–944. DOI: 10.1212/WNL.34.7.939 [PubMed: 6610841]
- Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *Journal of Gerontology*. 1982; 37:323–329. DOI: 10.1093/geronj/37.3.323 [PubMed: 7069156]
- Rascovsky K, et al. Rate of progression differs in frontotemporal dementia and Alzheimer disease. *Neurology*. 2005; 65:397–403. DOI: 10.1212/01.wnl.0000171343.43314.6e [PubMed: 16087904]
- Rascovsky K, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain: A Journal of Neurology*. 2011; 134:2456–2477. DOI: 10.1093/brain/awr179 [PubMed: 21810890]
- Rosen HJ, et al. Neuropsychological and functional measures of severity in Alzheimer disease, frontotemporal dementia, and semantic dementia. *Alzheimer Disease and Associated Disorders*. 2004; 18:202–207. [PubMed: 15592131]

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Table 1
Demographics (top) and assessments of cognition, neuropsychiatric symptoms, and functional status (bottom) in bvFTD and eoAD participants

DEMOGRAPHICS				
Mean years ± SD	N	bvFTD	eoAD	<i>p</i> ¹
Age	20	60.8 ± 10.9	59.0 ± 4.9	n.s.
Education	20	15.7 ± 2.3	16.3 ± 2.0	n.s.
Disease duration	20	4.4 ± 3.5	3.8 ± 2.0	n.s.
No. participants				
Men	20	11	9	n.s.
Right-handed	19	17	20	n.s.
Married	20	16	20	n.s.
White	20	18	23	n.s.
ASSESSMENTS				
Mean ± SD	N ^a	bvFTD	eoAD	<i>p</i> ¹
MMSE	20	24.50 ± 4.35	23.30 ± 4.82	n.s.
MOCA	14	18.07 ± 6.04	16.92 ± 5.78	n.s.
NPI	18	5.94 ± 2.51	3.08 ± 2.24	<.001
FAQ	16	18.50 ± 6.67	12.04 ± 5.90	0.003

¹Two-group *t*-test was used.

² χ^2 test was used; Behavioral variant frontotemporal dementia (bvFTD); early-onset Alzheimer disease (eoAD); Functional Activities Questionnaire sum (FAQ); Mini-Mental State Examination (MMSE); Montreal Cognitive Assessment (MoCA); Neuropsychiatric Inventory sum of symptoms present (NPI); Not significant (n.s.); Standard deviation (SD).

^aNumber of subjects varied due to incomplete test data. Lower scores indicate greater impairment for MMSE (0–30) and MoCA (0–30). Higher scores indicate greater impairment for NPI (0–12) and FAQ (0–30).

Table 2
Analyses of FTLD-CDR individual items between bvFTD vs. eoAD participants

mean $\pm$ SD	bvftd (n= 20)	ead (n= 24)	<i>p</i>
Memory	0.80 $\pm$ 0.25	0.98 $\pm$ 0.31	0.045
Orientation	0.60 $\pm$ 0.50	0.65 $\pm$ 0.35	n.s.
Judgment & problem solving	1.60 $\pm$ 0.66	0.85 $\pm$ 0.23	<0.001
Community affairs	1.45 $\pm$ 0.67	0.73 $\pm$ 0.42	<0.001
Home & hobbies	1.50 $\pm$ 0.58	0.88 $\pm$ 0.49	<0.001
Personal care	0.90 $\pm$ 0.79	0.13 $\pm$ 0.34	<0.001
CDR sum	6.85 $\pm$ 2.10	4.21 $\pm$ 1.47	<0.001
Behavior, comportment, & personality	1.90 $\pm$ 0.31	0.42 $\pm$ 0.60	<0.001
Language	0.33 $\pm$ 0.37	0.52 $\pm$ 0.52	n.s.
FTLD-CDR sum	9.08 $\pm$ 2.12	5.13 $\pm$ 2.07	<0.001

Two-group *t*-test was used.

Behavioral variant frontotemporal dementia (bvFTD); Clinical Dementia Rating scale 6 item sum (CDR); Early-onset Alzheimer disease (eoAD); Frontotemporal lobar degeneration Clinical Dementia Rating scale 8 item sum (FTLD-CDR); Not significant (n.s.); Standard deviation (SD).

Higher scores indicate greater impairment (individual items scored from 0–3; CDR sum 0–18, FTLD-CDR sum 0–24).