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The Mini-Mental State Examination in Behavioral Variant Frontotemporal Dementia and Primary Progressive Aphasia

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There is little information regarding the usefulness of the Mini-Mental State Examination (MMSE) for tracking progression of non-Alzheimer's disease dementias. This study examined the utility of the MMSE in capturing disease severity in the behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA), 2 nonamnestic clinical dementia syndromes. Retrospective data from 41 bvFTD and 30 PPA patients were analyzed. bvFTD patients' change in MMSE scores over time was significantly correlated with change over time on a measure of activities of daily living. In contrast, PPA patients' MMSE scores showed greater decline over time than scores on the activities of daily living scale. Results suggest that the MMSE score, heavily dependent on language skill, overestimates dementia severity in PPA patients. However, the score may be a more accurate measure of functional impairment in bvFTD due to the influence of their executive function and attentional deficits on MMSE performance.

Keywords: Mini-Mental State Examination; frontotemporal dementia; primary progressive aphasia; activities of daily living

The Mini-Mental State Examination (MMSE)[1] is a commonly used measure for gauging disease severity and dementia progression in Alzheimer's disease (AD). It includes items that measure orientation, attention, working memory, executive function, language, and immediate and delayed verbal recall.[2] All items are virtually dependent on comprehending verbal instructions and responding verbally, by speaking or writing. Studies have shown that over time, patients with AD show a steady decline in their MMSE scores.[1,3] However, there has been little research on the utility of this measure to track progression in non-AD dementias.

Frontotemporal lobar degeneration (FTLD) gives rise to 2 major clinical dementia syndromes that are characterized either by behavioral or by language deficits rather than by a primary amnesia.[4] The first, referred to as behavioral variant frontotemporal dementia (bvFTD), is associated with progressive behavioral changes in personal and social conduct, emotional reactivity, and degree of insight, as well as with executive dysfunction.[5] The second major presentation is known as primary progressive aphasia (PPA)[6] and is characterized by progressive loss of

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language function. The language loss can take one of several different forms that have been referred to as agrammatic, semantic, and logopenic.[7] Given the differences in the salient symptoms of bvFTD and PPA, it is likely that patients in each group could fail MMSE items for different reasons.[8] Thus, patients with bvFTD could fail due to an "economy of effort,"[9] poor persistence,[10] inability to shift from one task to another,[11] and/or impairments in working memory.[12] These cognitive skills are also important for most of the instrumental activities of daily living (ADL). In contrast, patients with PPA who have intact memory, executive functions, and attention may fail items only because of their aphasia, which is less limiting for most ADL compared with, for example, amnesia.

Alternative measures of dementia severity for staging and tracking disease are the questionnaires used for survey of ADL.[13,14] These measures typically sample the skills that a person needs to live independently. Assessment of ADL is essential in the diagnosis of dementia, as a reduction in functional ability is a core diagnostic criterion for any dementia syndrome according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[15,16] The skills of ADL are usually divided into 2 types: basic (eg, bathing, dressing, and eating) and instrumental (eg, money management, shopping, planning, and using transportation).[17] However, many of the early ADL scales emphasized the impairment related to physical decline rather than cognitive decline and were therefore unsuited for use in a population with early dementia.[18] The Activities of Daily Living Questionnaire (ADLQ)[18] was developed specifically for use in early dementia and has shown to be effective for the detection of functional decline in both AD and non-AD dementias.[14,18]

A number of studies have used the MMSE to measure the rate of cognitive decline in patients with FTLD. One study found that patients with bvFTD displayed an average annual decline of 6.7 points on the MMSE, significantly greater than the 2.3-point annual decline exhibited by patients with AD.[19] Additionally, nearly half the patients with bvFTD in that study also showed a loss in basic ADL over 1 year, and these patients showed significantly greater decline in MMSE scores than patients who maintained ADL over the same time period. In contrast, other studies have reported that patients with bvFTD showed less of a decline on the MMSE than patients with AD.[20] However, they noted that MMSE scores dropped dramatically when patients manifested symptoms of apathy and mutism, indicating that the MMSE may be inappropriate for tracking disease-related cognitive decline in the later stages of the illness.

Very recently, rate of cognitive decline measured by the MMSE has been compared in the language and behavioral variants of FTLD and in AD patients.[21] Both FTLD variants demonstrated significantly greater cognitive decline, as measured by the MMSE, than patients with AD, with no significant differences between the 2 FTLD variants. Thus, results examining cognitive decline in non-AD dementias using the MMSE have demonstrated variable results.

Given some of the limitations of the MMSE for measuring cognitive decline in non-AD dementias, measurements of ADL may be more reliable in tracking disease severity and progression in these nonamnestic syndromes.[22] Although a number of studies have compared the rate of decline on the MMSE between AD and the variants of FTLD,[19,21] no studies have compared rates of decline in bvFTD and PPA as measured by the MMSE versus a measure of ADL. The current study compared the rates of decline as measured by the MMSE and by the ADLQ in bvFTD and PPA to determine whether they are similar. It was hypothesized that the MMSE may overestimate dementia severity in PPA because of its reliance on the integrity of language.

Methods

Subjects

Archival data were analyzed from 41 patients with bvFTD and 30 patients with PPA who were enrolled in the Clinical Core of the Cognitive Neurology and Alzheimer's Disease Center (CNADC) at Northwestern University. All subjects were enrolled into the registry using a protocol approved by the Institutional Review Board at the Northwestern University, and all subjects had given written informed consent. All subjects were followed on an annual basis as part of the procedures of the CNADC Clinical Core. Diagnosis of bvFTD was determined by consensus according to the criteria outlined by Neary et al[4] and was based on neuropsychological test performance and a comprehensive neurological evaluation. None of the

Table 1. Sample Demographics

	Groups			
	bvFTD (n = 41)		PPA (n = 30)	
Demographic Variables	Median	25th-75th percentile	Median	25th-75th percentile
Age (y)	61	56-70[a]	67	62-72
Education (y)	16	12-16	16	14-16
Symptom duration (y)	3	2-4	4	2-5
MMSE (total = 30)	23	18-27	24	21-27
ADLQ (0%-100%)	27	19-40[b]	13	8-22

Note: bvFTD = behavioral variant frontotemporal dementia; PPA = primary progressive aphasia; MMSE = Mini-Mental State Examination; ADLQ = Activities of Daily Living Questionnaire.

a. Patients with bvFTD were significantly younger than those with PPA ($P < .05$).

b. Patients with bvFTD scored significantly higher on the ADLQ than those with PPA (ie, greater impairment) ($P < .01$).

patients with bvFTD had aphasia. Diagnosis of PPA was also based on neurological and neuropsychological evaluations and was made according to the criteria outlined by Mesulam.[23] Patients with any form of aphasia were included, and no attempt was made to further subtype the PPA group. The average duration of illness at the time of baseline evaluation was approximately 3.5 years for both the groups.

Procedures

All subjects had been administered an MMSE according to standard procedures.[1] Caregivers or study partners, defined as the individual with the most frequent contact and/or primary responsibility for the patient, completed the ADLQ.[18] This measure has been shown to be a valid and reliable assessment tool for measuring basic and instrumental ADL in dementia and comprises 6 subscales: self-care, household care, employment and recreation, shopping and money, travel, and communication. Total and subscale scores are calculated, with levels of impairment as follows: 0% to 33% = none to mild impairment, 34% to 66% = moderate, and >66% = severe (see Johnson et al[18] for details on scoring and administration). For the purpose of the present study, only the total percentage scores were analyzed. Distinctive patterns of performance on the subscales in patients with bvFTD, PPA, and AD are reported elsewhere.[14]

Data Analysis

An annualized rate of change score was calculated for each measure by subtracting the patient's score at his or her last visit from the score at the first (baseline) visit and dividing by the number of years between visits. Length of time between baseline and follow-up visit ranged from 1 to 3 years. Because of the nonnormality of the data, nonparametric tests were used for analyses. Wilcoxon rank sum tests were performed to compare the 2 groups on demographic characteristics and baseline assessment measures. The relationship between the rate of change over time on the MMSE and ADLQ in each of the groups was examined using Spearman's correlation coefficients and Wilcoxon signed ranks tests.

Results

Table 1 summarizes the demographic variables for the 2 subject groups. Individuals with PPA (median age = 67 years) were significantly older than those with bvFTD (median age = 61 years; $W_s = 1271.5$; $P < .05$). There were no significant differences in levels of education, duration of illness, or MMSE score at baseline between the bvFTD and PPA groups. Baseline ADLQ scores were significantly different, with bvFTD patients (median score = 27%) more impaired than PPA patients (median score = 13%; $W_s = 747.5$; $P < .01$); however, the scores of both the groups fell in the "none to mildly impaired" range (ie, 0%-33%).

In the bvFTD group, there was a significant correlation between subjects' change scores on the MMSE and ADLQ ($r = 0.348$; $P < .05$). Furthermore, direct comparison of the mean percent change on both measures showed no significant difference ($z = -0.667$, not significant). The correlation between the MMSE and the ADLQ change scores was not significant in the PPA group ($r = 0.188$, not significant). Moreover, the MMSE percent change score differed significantly from the percent change score on the ADLQ in this group ($z = -2.088$; $P < .05$) (Figure 1).

Discussion

The present study was conducted to determine whether the MMSE, a reliable measure of cognitive

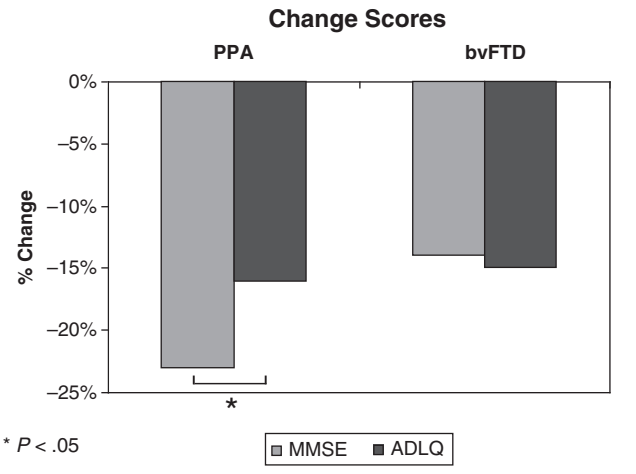

Figure 1. Annualized percentage change on the MMSE and the ADLQ in PPA and bvFTD subjects. bvFTD = behavioral variant frontotemporal dementia; PPA = primary progressive aphasia; MMSE = Mini-Mental State Examination; ADLQ = Activities of Daily Living Questionnaire.

impairment and progression of dementia severity in AD,[24] is similarly meaningful in bvFTD and PPA. Due to the nonamnestic nature of the cognitive and behavioral deficits in these 2 syndromes, it was predicted that the MMSE may not accurately reflect dementia severity, as would a measure of ADL. Results of the present study demonstrated that patients with bvFTD show decline on both the MMSE and the ADLQ to a similar degree. However, in patients with PPA, the MMSE suggested a steeper rate of decline than was shown by the ADLQ. Thus, the MMSE overestimated the level of dementia severity in this group.

Previous research has suggested that the cognitive and behavioral changes that accompany frontal lobe dysfunction in bvFTD mediate the functional changes measured by ADL scales.[19] The results of this study support this idea and suggest that both the MMSE and ADLQ may be adequate measures to track severity and disease progression in bvFTD. This finding is also supported by previous results, which showed greater decline on the MMSE in patients who lost their ability to complete ADL over a 1-year period than in those who retained those abilities.[19] This suggests that the MMSE is effective in detecting and staging the symptoms that accompany frontal lobe deterioration, which include behavioral disinhibition as well as, attention, working memory, and executive function deficits.

In contrast to the present findings, another study found no relationship between the MMSE and a measure of ADL, the Disability Assessment for Dementia (DAD)[25] in patients with bvFTD and PPA.[17] There are a number of reasons for this discrepant finding. First, the DAD was initially created for use in patients with AD, which may make it unsuitable or less suitable, especially in early stages, for use in patients with other dementia syndromes that present with different symptomatology. Additionally, the study had a smaller sample size (15 bvFTD and 10 PPA patients) compared to the present study.

The MMSE registered a higher degree of severity and greater change over time than the ADLQ in patients with PPA. One explanation for this result is that the MMSE is highly reliant on intact language abilities, which has been suggested in previous studies.[26] Given that PPA patients primarily have difficulty in the language domain early in the disorder, the MMSE may overestimate the degree of dementia severity in this population. One study found that certain items on the MMSE, specifically in the verbal domain, such as word registration and recall, object naming, repetition, and carrying out verbal commands, were problematic for PPA patients.[27] These items represent 12 of the possible 30 total points a subject can obtain on the MMSE, which can account for significantly lower scores on this measure.

The present findings also differ from those of the only other study to date that examined annualized scores on the MMSE in the behavioral and language variants of FTLD. In the study by Chow et al,[21] no differences were observed in the rate of change between the 2 groups. Differences in sample size, duration of illness, and length of time at follow-up are all variables that could have resulted in discrepancies between that study and the present study. There were 25 patients with the behavioral variant and 19 patients with the language variant,[21] which is approximately half the size of the present sample. Data on duration of illness were not reported for that study. Additionally, all follow-up visits were conducted within a year of the subject's baseline visit, which may not have been enough time to observe unique changes in these 2 groups.

Limitations of the present study include the retrospective nature of the data analysis, which limits the extent to which more detailed analysis can be conducted on the measures. An examination of the individual items on the MMSE in both groups could have yielded more information on the specific deficits that led to poor performance on this measure; however, data were not archived in the database

with this degree of detail. Another limitation is that the ADLQ is a caregiver-completed measure of functional ability, which is a subjective measure highly reliant on interpretation by family members and not on direct patient performance. Yet another issue surrounds reliance on annualized change scores to measure change over time, which only uses scores from the first and last visits. The method of Best Linear Unbiased Predictors (BLUPs),[28] which uses all available data points in estimating annualized rate of change for each subject, is a more statistically sound method for measuring change over time; however, a relatively small sample size and the unavailability of subject data at every data point made it difficult to use this method. Efforts are being made to apply this method to analyze additional data.

Findings from the current study suggest that the highly verbal nature of the MMSE may be problematic when used alone in patients with PPA, as it may not accurately represent functions that are preserved. The ADLQ provides an objective method for obtaining caregivers' observations on functional ability in daily living activities in both patients with PPA and bvFTD and may be a useful adjunct to track overall disease severity and progression in these populations, especially in patients with PPA.

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