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Neuropsychological testing in pathologically verified Alzheimer's disease and frontotemporal dementia: how well do the Uniform Data Set measures differentiate between diseases?

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Abstract

Background/Aims—Differences in cognition between frontotemporal dementia (FTD) and Alzheimer's disease (AD) are well described in clinical cohorts, but have rarely been confirmed in studies with pathological verification. For emerging therapeutics to succeed, determining underlying pathology early in the disease course is increasingly important. Neuropsychological evaluation is an important component of the diagnostic workup for AD and FTD. Patients with FTD are thought to have greater deficits in language and executive function while patients with AD are more likely to have deficits in memory.

Objectives—To determine if performance on initial cognitive testing can reliably distinguish between patients with frontotemporal lobar degeneration (FTLD) and AD neuropathology. Additionally, are there other factors of the neuropsychological assessment that can be used to enhance the accuracy of underlying pathology?

Methods—Using a logistic regression we retrospectively compared neurocognitive performance on initial evaluation of 106 patients with pathologically-verified FTLD (pvFTLD), with 558 pathologically verified AD (pvAD) patients from the National Alzheimer's Coordinating Center (NACC) using data from the Uniform Dataset (UDS) and the neuropathology dataset.

Results—As expected, pvFTLD patients were younger, demonstrated better memory performance, and had more neuropsychiatric symptoms than pvAD patients. Other results were less predictable: pvFTLD patients performed better on one test of executive function (trail making test part B) but worse on another (digit span backward). Performance on language testing did not strongly distinguish the two groups. In order to determine what factors led to a misdiagnosis of AD in patients with FTLD, we further analyzed a small group of pvFTD patients. These patients demonstrated older age and lower NPIQ counts compared with accurately diagnosed cases.

Conclusions—Other than memory, numerical scores of neurocognitive performance on the UDS are of limited value in differentiating FTLD from AD at the initial visit. These results highlight the difficulty of obtaining an accurate early diagnosis of FTLD and argue for adding supplemental tests to those included in the UDS to assess cognition in FTD and AD patients.

Introduction

Frontotemporal dementia (FTD) is the clinical manifestation of a number of different pathological processes resulting in focal atrophy of the frontal or temporal lobes. The term frontotemporal lobar degeneration (FTLD) is used to capture the pathological processes that cause the clinical syndrome of FTD. Three clinical subtypes of FTD are now strongly associated with FTLD: a behavioral variant and two types of primary progressive aphasia¹. After Alzheimer's disease (AD), FTLD is the second most common neuropathological finding associated with young onset dementia. Although advances in biomarkers have improved diagnostic accuracy, the considerable phenotypic overlap that exists between AD and FTD results in a substantial percentage of patients being misdiagnosed, especially early in the disease course². Currently, neuropathological examination remains the gold standard of diagnosis for both diseases. Improving the accuracy rates of a clinical diagnosis of AD and FTD remain a significant challenge in the field of dementia given the differences in treatment, prognosis, and heritability. High misdiagnosis rates also represent a major impediment to the development of much needed molecular-based therapies.

Neuropsychological assessment is an important element of the workup used to diagnose FTD and AD. Traditionally, the neurocognitive profiles of FTD is associated with early and significant impairments in language and executive functioning while AD is characterized by early deficits in episodic memory not normalized by cues³. Differences in the behavioral dimension associated with AD and FTD have also been described⁴. While a number of studies have compared the neuropsychological profiles between FTD and AD in clinically diagnosed cohorts^{5,6,7,8,9}, fewer studies have looked at neuropsychological testing in subjects with pathological-verification^{10,11,12,13}. Studies verifying clinical-pathological correlations are greatly needed.

The National Alzheimer's Coordinating Center (NACC) database represents a unique opportunity to investigate clinical symptoms while ultimately knowing final pathology. Among many items included in the database is a uniform data set (UDS) composed of a brief neuropsychological test battery (NTB) and the Neuropsychiatric Inventory Questionnaire (NPI-Q)¹⁴ alongside other measures. In this study we retrospectively compared the results of cognitive testing and NPI-Q scores from the first clinical visit in patients with pathological verified AD (pvAD) and pathologically verified FTLD (pvFTLD). We were also interested in determining the accuracy of an initial clinical diagnosis of FTD, and in those misdiagnosed, if certain elements of neuropsychological testing could be used to improve diagnostic accuracy. Overall, the aim of this study was to assess the ability of the UDS to differentiate these common forms of dementia at initial clinical presentation.

Methods

The NACC serves as a data repository from more than 30 past and present National Institute on Aging Alzheimer's Disease Centers (ADCs). Included in the NACC is a Uniform Data Set that includes standardized demographic, cognitive, and behavioral information as well as a clinical diagnosis. Clinical diagnosis for each ADC patients is based on standard criteria but varies according to each ADC's diagnostic protocol. Included in the NACC is a

neuropathology data set (NP) containing standardized neuropathology data¹⁵. The NP permits each individual site's pathologist to attribute a single “primary diagnosis” and multiple “contributing diagnosis” to each autopsied brain. The NP allows for the discretion of each ADC site in making the diagnostic attribution and does not impose that a specific criteria be used (i.e. CERAD, NIA/Regan Institute, ADRDA/Khachaturian). The NACC also collects data on patients with dementias from non-AD etiologies.

For this study, neuropathological data from the NP were cross-referenced with clinical information abstracted from the UDS. The data were from the NACC sample after initiation of the UDS in September 2005, locked in March 2014. In our sample, we included all cases of pvFTLD and pvAD who had completed the NTB battery during their initial clinical visit. In an attempt to control for dementia severity, scores on initial MMSE were compared between the two groups. Because no significant differences were detected, all patients were included in the analysis.

UDS scores from the first clinical visit were analyzed. The NTB includes the following tests: Digit Span Forward (Wechsler Memory Scale-Revised) to test attention; Digit Symbol (Wechsler Adult Intelligence Scale-Revised) and Trail Making Test Part A to test processing speed; Trail Making Test Part B (TMB) and Digit Span Backward (Wechsler Memory Scale Revised) to test executive functioning; Logical Memory Story A, Parts I (LMI) and II (LMII) to test memory; and The Boston Naming Test (30 odd items) and two word generation tasks (vegetables and animals) to test language and word generation¹⁴.

Clinical diagnoses within the NACC are made by expert clinicians at each of the center according to published research criteria. Within the NACC coding scheme there is a code for “primary diagnosis”. To define the pathological diagnosis of our groups we started with those coded as having a primary neuropathological diagnosis of FTLN (NACC database code NPPFTLD=1) or AD (NACC database code = NPPAD). We excluded patients where FTLN or AD were considered “contributing diagnoses”. For clinical diagnoses, we only included primary diagnoses.

Analysis Plan

We used logistic regression to assess the likelihood of each test in separating the two pathological groups. Age and education were used as regressors given their potential influence on test scores. A logistic regression model using pathological diagnosis as a classification (FTLD or AD) as the outcome and raw scores of neuropsychological measures and number of symptoms endorsed on the NPIQ as predictors, as well as, age and years of education was fit. Odds ratios and associated 95% confidence interval for each predictor were evaluated to determine the relative influence of each predictor on group membership. Although typically used in generating models to predict group membership, logistic regression models can alternatively be used to simultaneously test for group differences among a set of variables when two groups are being compared without increasing risk of false-positive errors from multiple comparisons and with fewer underlying assumptions¹⁶.

Results

Clinical Characteristics and Neurocognitive Test Performance

106 patients with pvFTLD were compared with 558 patients with pvAD. A test of the full model against a constant only model fit using the original data was significant ($X^2 = 192.54$; $p < .0001$, Nagelkerke $R^2 = .41$). Potential collinearity was addressed: the tolerance and variance inflation factors were acceptable. Condition indices in excess of 20 were further evaluated, and variance proportions revealed significant collinearity only between LM I and LM II. Subsequently, LM I was excluded allowing us to retain the test of delayed memory, i.e., LM II.

The variables included in the analysis are included in Table 1. Of the entered variables, several showed significant differences between groups in the pooled model. pvFTLD patients performed better on TMB, and LM II. pvFTLD patients performed more poorly on Digit Span Backwards, Semantic Fluency, and had a larger number of NPI-Q symptoms.

Diagnostic Accuracy

Comparisons between initial clinical diagnosis and pvFTLD and pvAD are presented in Figure 1. When combining both language and behavioral variants, an initial clinical diagnosis of FTD accurately predicted FTLT pathology approximately 57% of the time. 18% of patients diagnosed with AD were ultimately found to have FTLT pathology. An initial clinical diagnosis of AD was found to accurate in 70% of patients. A variety of other initial clinical diagnoses turned out to have AD pathology at autopsy.

Clinical Characteristics of Misdiagnosed pvFTLD Cases

A sizeable number of patients harboring FTLT pathology had been misdiagnosed with AD at their initial visit. In order to better understand the clinical characteristics that may distinguish this group from their counterparts with FTLT who were accurately diagnosed, an additional analysis was performed. We used the same logistic regression model described above, however, only those variables that were statistically significant in the larger model were included in the analysis (age, LMII, Digit Span Backwards, Animal Fluency, TMB). While this is admittedly underpowered, it allows for exploration of the clinical differences between accurately diagnosed and misdiagnosed patients and was thus considered important, even at the exploratory level.

In this analysis significant differences were only seen in two variable: (a) age—pvFTLD patients initially diagnosed clinically with AD were significantly older (mean age of 76.51 years old compared to 64.16 years old)—and (b) NPI-Q total symptom score—misdiagnosed pvFTLD patients had fewer neuropsychiatric symptoms (odds ratio 1.37, $p = .003$, CI: 1.050-1.792)—than accurately diagnosed patients.

In comparing the neuropsychiatric profile of those were accurately diagnosed compared to those who were misdiagnosed, three symptoms emerged as being more common in the accurately diagnosed FTLT group: aberrant motor changes ($p = .001$), apathy ($p = .002$), and delusions ($p = 0.42$). There were no significant differences in the frequency of appetite

changes, nighttime behaviors, irritability, disinhibition, anxiety, elation, agitation, and hallucinations. No NPI-Q symptoms were more common in the misdiagnosed FTLN patients.

Discussion

In the absence of definitive biomarkers, there is great interest in defining phenotypic signatures of FTLN, especially early in the disease course when molecular based therapies are more likely to be effective. Utilizing the NACC database, this study retrospectively looked for differences in initial neuropsychological assessment in a large group of patients with later pathological verification of either FTLN or AD. To the best of our knowledge this study represents the largest comparison of neurocognitive test performance with pathological verification. As expected, we found that pvFTLN patients present at a younger age, report a greater number of neuropsychiatric symptoms, and perform better on memory tests than pvAD patients. Other results were less predictable with pvFTLN patients performing better on one test of executive function (TMB) and worse on another (reverse digit span). Additionally, performance on language testing did not clearly separate the two groups. In general, with the exception of memory, the UDS did not define distinct patterns of neurocognitive performance between the two groups.

A number of studies have reports that AD and FTLN have different neuropsychological profiles with the most robust differences seen in executive function⁹, visuospatial abilities^{17,13}, language¹⁰, and memory^{11,13}. In the current study we found significant differences in the expected direction only in memory. Executive measures showed more variable findings that might be expected. Performance on TMB, with pvFTLN taking less time to complete the task, showed the reverse finding than would be expected. The sensitivity of this measure in detecting executive dysfunction in FTLN is relatively unknown as it has not been widely reported in FTLN cohorts¹⁸. Several studies have reported that certain aspects of executive function as more severely affected than others—particularly decision making more than working memory^{19,20}—and it is possible that the tests included in UDS are not sensitive to accurately capture the executive dysfunction in FTLN. This has led some authors to advocate for characterizing performance across a full range of executive abilities and for the qualitative assessment of performance rather than simply comparing scores²¹.

Despite published and validated criteria for FTD, many patients are initially misdiagnosed. In this study we found that only 57% patients with FTLN neuropathology were correctly identified as having a FTD (combining both language and behavioral variants) at their initial visit. Notably, 1 in 5 patients with FTLN were initially misdiagnosed clinically as AD. When we compared this group (i.e. those misdiagnosed with AD but ultimately having FTLN neuropathology) to those who were accurately diagnosed, we found that misdiagnosed patients were significantly older (on average 12 years older) and reported fewer neuropsychiatric symptoms. Although we assumed that this group of FTLN patients presented with an AD “phenotype” (memory loss) this was not necessarily the case as both groups performed comparably on neurocognitive testing. This finding suggests that a percentage of FTLN patients present later in life and with a milder behavioral phenotype.

Memory testing is likely useful in distinguishing this group from patients with underlying AD neuropathology.

This study has several limitations. First, the NACC database lacks detailed neuroanatomical information on the localization of pathological changes. Because of this, when we analyzed neurocognitive performance of patients with FTLN, we were unable to separately assess patients with left temporal pathology from those with orbitofrontal or right temporal pathology. As a result, all patients with underlying FTLN pathology (whether or not they presented with a language or behavioral variant phenotype) were analyzed together. This is important because it is likely that specific network disruption rather than the type of cellular change that drives phenotypic expression. Second, the concept of primary progressive aphasia has evolved significantly during the period of data collection. Three variants of primary progressive aphasia are now recognized, including one variant—the logopenic form of primary progressive aphasia—that is typically caused by AD. Patients diagnosed with logopenic aphasia are coded as “PPAOTHR” in the NACC database, a clinical criteria that also includes other language descriptions such as “anomic”. Consequently, we were unable to analyze patients initially diagnosed with logopenia as part of the AD group. Based on the small number of patients diagnosed with “PPAOTHR” this is unlikely to have had a significant impact on our results. Finally, new staining techniques for FTLN have greatly improved over the past five years. In particular, pathologists are much better able to characterize the tau negative forms (TDP-43 and FUS varieties) that cause about 50% of all FTLN cases. This study utilized analyzed retrospective data from the NP database that, in many cases did not have access to these newer staining techniques.

Forthcoming research involving FTD, including analysis of the NACC FTLN module that was introduced in 2012 adding pathological data in 2014, may overcome many of the limitations of the current study, including providing more thorough clinical description and updated pathological definition. For now, emphasis in both clinical and research settings on adding supplemental tests to those included in the UDS to assess cognition in FTD and AD patients, and continued emphasis on behavioral measures will be important in attempting to optimize the diagnosis of and research into these two common forms of dementia.

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Figure 1.

Pie charts to demonstrate initial visit diagnoses of patients diagnosed at autopsy with FTL D (left) and AD (right). For parsimony, we grouped the NACC clinical diagnostic codes. AD_Group includes PROBAD (probable AD), POSSAD (possible AD), MCIAM (MCI amnestic). FTD included only behavioral FTD. PPA_Group includes PPAPH (primary progressive aphasia), SEMDEMAN (semantic dementia-anomia plus word comprehension), SEMDEMAG (semantic dementia agnosia variant), PPAOTHR (primary progressive aphasia other-logopenic, anomic, etc.). Park_Group includes PARK (Parkinson's disease), PSP (progressive supranuclear palsy), CORT (corticobasal degeneration). DEMUN includes only that diagnosis (Dementia of undetermined etiology), similarly, DLB (dementia with Lewy bodies), VAS (vascular dementia) and NORMCOG (normal cognition) include only their own diagnostic category.

Table 1
Demographic, cognitive, and neuropsychiatric variables included in the logistic regression

	pvFTLD	pvAD	Significant difference? P value	Odds Ratio	Confidence Interval
% women	39.4	43.9	ns		
Age at assessment	69.11 (11.58)	79.47 (10.02)	ns		
Age at autopsy	72.27 (11.96)	83.55 (10.02)	.0001	1.089	1.062-1.116
Years of education	17.56 (14.07)	16.20 (8.23)	ns		
MMSE score	24.65 (4.67)	24.36 (2.34)	ns		
LMII	5.86 (4.91)	4.21 (4.75)	.0001	.86	.808-.915
Digits Forward	7.48 (2.15)	7.43 (2.19)	ns		
Digits Backwards	4.59 (2.16)	5.21 (2.03)	.009	1.265	1.061-1.509
Digit Symbol	31.13 (12.64)	28.30 (13.05)	ns		
Animal Fluency	10.22 (5.17)	12.64 (5.06)	.0001	1.187	1.06-1.510
Vegetable Fluency	6.78 (4.07)	7.89 (3.86)	ns		
Trail Making Part A (sec)	55.22 (30.67)	62.91 (34.17)			
Trail Making Part B (sec)	174.86 (90.93)	201.38 (87.44)	.001	1.007	1.003-1.011
Boston Naming	21.01 (8.76)	22.34 (6.12)	ns		
NPI-Q Symptom Count	4.54 (3.09)	2.49 (2.33)	.0005	.815	.738-.899

Ns = not significant