Cognitive Measures Predict Pathologic Alzheimer Disease

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Background: Neuropsychologic testing is often used to infer neuropathologic processes, but clinicopathologic correlations for individual cognitive measures are based on a small number of published studies.

Objective: To examine the usefulness of the age- and education-adjusted Mayo Cognitive Factor Scales (MCFS) obtained at participants’ initial assessments for predicting the presence or absence of pathologic Alzheimer disease (AD).

Design: This was a longitudinal study of a cohort of elderly patients with and without cognitive complaints who were followed up until death. Mayo Cognitive Factor Scales age- and education-adjusted standard scores from the participants’ initial evaluations were used to calculate classification accuracy statistics for neuropathologic AD diagnosis obtained approximately 6 years after testing. Subjects with non-AD diagnoses or substantial non-AD-related changes were excluded from the study.

Setting: Academic medical center.

Participants: One hundred two participants were evaluated clinically and underwent neuropathologic examination at autopsy. All were part of the Mayo Clinic Alzheimer’s Disease Patient Registry or Alzheimer Disease Research Center.

Results: All Mayo Cognitive Factor Scale scores were significantly correlated with AD criteria. Logistic regression modeling including Mayo Cognitive Factor Scales Verbal Comprehension and Retention indices revealed high positive predictive value with moderate sensitivity and specificity for pathologic AD.

Conclusion: Neuropsychologic test scores at initial evaluations were predictive of pathologic AD.

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Neuropsychologic testing is widely used in the clinical evaluation of patients with suspected dementia. Extensive data exists on the relationship between neuropsychologic test results and the clinical diagnoses of neurologic disease, but fewer studies have explored the predictive value of cognitive measures for autopsy-proved cases or for specific neurologic diseases. The validity of diagnostic neuropsychologic assessment is based on its association with neuropathologic findings.

During the past 13 years, we have performed prospective clinical evaluations that included neuropsychologic testing and have encouraged patients to consent to autopsy at death. More than 400 patients who underwent at least 1 clinical evaluation have been examined post mortem, making it possible for us to address the question: How well do neuropsychologic tests predict pathologic Alzheimer disease (AD)?

Although neuropathologic diagnoses are considered the standard against which all antemortem predictors must be considered, important challenges complicate such analyses. First, the lag between initial neuropsychologic testing and death may be many years; intervening events may invalidate attempts to correlate neuropsychologic results with neuropathologic findings. Second, neuropathologic examination of patients thought to have uncomplicated AD often reveals other abnormal findings (eg, Lewy bodies) that confound the correlation between cognitive changes and AD-related changes. We limited the effect of these 2 issues by focusing on patients with dementia who from initial evaluation to death were free of other illnesses, in particular, obvious brain diseases other than clinical AD. Third, we restricted our analyses to subjects who had either no neurologic disease at autopsy or who had AD-related changes. These restrictions enabled us to explore the relationship between AD and
cognitive change without the confounding effects of other neurologic diseases. Our primary objective was to examine the usefulness of the age- and education-adjusted Mayo Cognitive Factor Scales (MCFS) obtained at participants' initial assessments for predicting the presence or absence of pathologic AD. Although using data obtained closer to autopsy (eg, final psychometric evaluation) would likely improve the association between cognitive performance and neuropathologic disease, data from patients' initial evaluations were selected as predictors to mirror the clinical situation as to when neuropsychologic evaluations may be of most clinical benefit (eg, enabling early diagnosis).

METHODS

The Mayo Clinic Institutional Review Board approved this study. All participants were enrolled in the Mayo Clinic Alzheimer's Disease Patient Registry or Alzheimer Disease Research Center. Participants were included in this study if they received a neuropsychologic assessment, a clinical diagnosis was made ante mortem, and neuropathologic examination was performed at autopsy.

Subjects with and without cognitive complaints were recruited from the Mayo Clinic Community Internal Medicine Department or the Department of Neurology. At the initial evaluation, each subject was seen by a study physician (D.S.K., B.F.B., or R.C.P.) who performed a neurologic examination and obtained a complete history. The neuropsychologic battery of tests was administered. All subjects with cognitive impairment and most healthy subjects underwent magnetic resonance imaging unless contraindicated, in which case they underwent computed tomography. Screening laboratory studies were also performed. At the completion of the assessment, evaluations were reviewed in a consensus conference consisting of neurologists (D.S.K., B.F.B., and R.C.P.), neuropsychologists (G.E.S. and R.J.L.), nurses, and geriatricians. A final clinical diagnosis was made for that visit based on all available information. Final clinical diagnoses of dementia were consistent with Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria16 and later with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria19. Diagnoses of AD fulfilled National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for AD.19 Subjects were seen multiple times and clinical diagnoses were made at each evaluation.

Participants were included in the clinical diagnosis group if a diagnosis of AD or normal was made at the last antemortem consensus meeting. Those having clinical diagnoses other than AD or normal were excluded from analyses. A neuropathologic diagnosis of AD was made in participants who met National Institute on Aging and the Reagan Institute Working Group criteria20 for intermediate or high likelihood of AD at autopsy, and a diagnosis of normal was made if they met National Institute on Aging and the Reagan Institute Working Group criteria for low likelihood of AD at autopsy. Clinical and pathologic groups were formed independent of one another; that is, a subject with a clinical diagnosis of normal may have had a neuropathologic diagnosis of AD. The mean interval between subjects' final clinical evaluation and pathologic diagnosis was less than 6 months. According to National Institute on Aging and the Reagan Institute Working Group criteria, 7 (7.4%) of 94 participants having a clinical diagnosis of normal were deemed to have intermediate or high likelihood for pathologic AD and 3 (3.2%) of 94 participants with clinical AD were found to have a low likelihood for pathologic AD at autopsy. As noted, subjects were excluded from the neuropathologic AD group if they were found to have significant involvement of any neuropathologic disorder other than AD. Data were available for 94 subjects having a clinical diagnosis and 102 subjects having a pathologic diagnosis. The sample size varied across groups because of missing cognitive data.

The MCFS age- and education-adjusted standard scores obtained during the initial cognitive evaluation were the primary independent variables used to differentiate between pathologically confirmed AD and normal status. The MCFS indices are derived from confirmatory factor analysis of concurrent administration in a large sample of healthy subjects of well-established cognitive instruments, including the Wechsler Adult Intelligence Scale–Revised,20 the Wechsler Memory Scale–Revised,21 and the Rey Auditory Verbal Learning Test.22 Five MCFS factors best described the cognitive abilities assessed by these instruments: Verbal Comprehension, Perceptual Organization, Attention/Concentration, Learning, and Retention.23 We also included the Mattis Dementia Rating Scale23 as a measure of overall severity of dementia.

Participants underwent, on average, 5 or 6 cognitive evaluations, and clinical diagnoses were made after each assessment. We report descriptive data for the study's primary independent variables for both clinical and pathologic AD. We restricted the predictive statistics by addressing only the MCFS score relationship with pathologic AD; however, this is the criterion standard and, unlike clinical diagnosis, is not influenced by the initial neuropsychologic evaluation.

RESULTS

Descriptive data are given for participants according to their last antemortem clinical diagnosis (normal vs AD) and their neuropathologic diagnosis (normal vs AD). As given in Table 1, age at death, age at testing, interval between testing and death, years of education, and sex composition did not differ for subjects with clinical or pathologic AD relative to their normal comparison groups. As expected, patients with clinical or pathologic AD scored lower on the Mattis Dementia Rating Scale, although their mean scores reveal their relatively mild clinical status during the initial evaluation. Group comparisons on all MCFS scores were also significant, with subjects with AD scoring lower on all variables (Table 2). Interval between initial testing and death did not differ for participants having a diagnosis of AD or normal.

Forward selection logistic regression models using age- and education-adjusted MCFS scores from initial evaluation and interval to predict pathologic AD determined approximately 6 years after the initial testing was significant ($\chi^2 = 27.7, P < .001$) and included interval along with the MCFS Verbal Comprehension and Retention factors. Overall accuracy was 74.7%, sensitivity was 73.0%, and specificity was 73.9%. Positive and negative predictive values were 89.5% and 50.0%, respectively.

COMMENT

This study examined the relationship between MCFS scores and AD-related changes by using scores obtained from patients' initial cognitive evaluations to predict a neuropathologic diagnosis of AD. The MCFS scores differed substantially between AD and normal groups determined clinically or pathologically. More important, MCFS scores
had moderately strong predictive value for neuropathologic AD (relative to pathologically confirmed normal status) despite an approximate 6-year interval between the initial assessment and death. These findings provide additional support for the moderately strong relationship between cognitive status and AD neuropathologic changes and for the predictive utility of various MCFS indices.

In addition, the results provide additional evidence for the predictive value of language-based and memory retention measures for identifying persons who have pathologically confirmed AD. The predictive value of a memory retention measure was not surprising because the strong relationship between memory and AD is well documented. Initial learning and memory deficits are a hallmark clinical feature of AD and are functionally associated with the early hippocampal lesions observed in the typical progression of neurofibrillary tangle pathology.

The association of the Verbal Comprehension factor and pathologic AD, however, was more surprising, especially given previous findings that the MCFS Verbal Comprehension index was the least sensitive factor score for clinical AD. In retrospect, the Verbal Comprehension predictive power may relate to isocortical disease present in our pathologic AD group that was not present in our pathologic normal group. Even during initial testing (6 years before pathologic diagnosis), participants composing our pathologic AD group may have had significant isocortical disease (eg, Braak stage IV or higher), negatively affecting their performance on measures more resistant to neurologic disease (eg, overlearned verbal information). Those confirmed to be pathologically normal would not have had isocortical disease during initial assessment.

Other research has demonstrated a link between performance on memory- and language-based tasks in patients with AD with relatively greater pathologic findings in the temporal lobe than in other brain regions. The selection criteria may have increased the odds that our subjects with AD had relatively greater temporal lobe disease compared with that in other brain regions because we excluded patients with coexisting non-AD-related disor-
ders. This method may have inflated the predictive value of memory and language tests for AD diagnosis.

The exclusion of participants with non-AD-related disorders from our analyses reduced the generalizability of our results to clinical practice. In the clinic, we do not have the luxury of evaluating only patients with circumscribed or isolated neuropathologic findings, because many are found to have an admixture of pathologic changes. Our primary goal, however, was to establish the existence of the MCFS predictive power for the presence of AD-related changes; that is, we sought to establish the MCFS as a sensitive marker rather than a specific marker for AD. It was reasonable to eliminate other neuropathologic diseases from analysis. We also acknowledge that the high base rate of AD in this investigation increased the positive predictive value and diminished the negative predictive value of the MCFS scores. However, our base rate, however, may reasonably correspond to the base rate of AD in subjects undergoing neuropsychologic evaluation because of memory complaints.

Studying the diagnostic validity of our clinical instruments not only strengthens our trust in measures that prove to have a strong relationship with well-defined, objective criteria but corrects misperceptions regarding the diagnostic usefulness of other measures that contribute little to the diagnostic process. Ideally, this type of data will help guide clinicians' test selection and improve diagnostic accuracy in clinical practice.

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