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Methods to Improve the Detection of Mild Cognitive Impairment

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In the United States today, approximately 12 percent of individuals age 65 and over and 0.8 percent of persons 45–65 years old have Alzheimer's disease (AD) or a related disorder (ADRD)[1]. ADRD refers to all disorders that can lead to mild cognitive impairment (MCI), which is typically followed by dementia. MCI has been defined in a variety of ways, and there is no universally accepted standard. However, all definitions share the feature of cognitive impairment (usually just one) that does not impair instrumental activities of daily living (e.g., shopping, finances, cooking, household maintenance and finding familiar locations). Dementia is defined as the presence of two or more areas of cognitive impairment that affect instrumental activities of daily living at the very least.

The most common dementia-related disorders are AD (55–70 percent), cerebrovascular dementia (15–25 percent), Lewy body disease and Parkinson's disease (10–15 percent), frontal lobe dementia (5–10 percent) and traumatic brain injury (about 5 percent)[2]. A comprehensive multifactorial evaluation including clinical assessment, laboratory testing and imaging is typically used to diagnose ADRD. The earliest clinical stage of ADRD is classified as MCI. During this stage, an individual's most complex abilities may be compromised but higher-order instrumental activities of daily living such as traveling, paying bills, doing laundry and balancing a checkbook are spared. Because there is irreversible loss of function for every month that mild to moderate AD goes untreated, and because cholinesterase inhibitor treatment reduces the rate of cognitive impairment in AD patients treated for five years by about 50 percent[3,4], it is important to detect, diagnose, and treat AD as early as possible.[5,6,7,8,9]

MCI and dementia can be measured by using a variety of standardized tools, one of which is the clinical dementia rating (CDR) scale. The clinician using this scale interviews the patient and family, assigns a severity score to each of six CDR subcategories (memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal hygiene), and then applies standard scoring rules to obtain an overall severity score. A CDR score of zero (0) suggests normal aging, a score of 0.5 indicates MCI, and scores of 1, 2, and 3 indicate mild, moderate, and severe dementia, respectively. A person with mild dementia (MD) is impaired in performing instrumental activities of daily living such as traveling, shopping, paying bills, keeping house and cooking. A person with moderate dementia is impaired in basic activities of daily living such as dressing, bathing and toileting.

Although current methods of detecting moderate dementia in community-based clinical practices are reasonably accurate, they do not sensitively detect MCI and often do not detect MD. This insensitivity is because a person with MCI or very MD experiences subtle memory problems greater than normally expected with aging but may not show other symptoms of dementia such as impaired judgment or reasoning. In fact, 67 percent of individuals are moderately demented at the time of first diagnosis.[10,11]

The difficulty in detecting MCI and, in many cases, MD is largely because of the insensitivity of the most commonly used screening test in clinical practice, the MiniMental Status Examination (MMSE). The MMSE is a brief test of several cognitive abilities with a maximum score of 30 points. One of the larger studies designed to differentiate individuals with MCI from those with normal aging showed that the MMSE detected only 30 percent of 244 subjects classified as MCI according to a CDR score of 0.5.[12,13] This showed that more sensitive screening tests are needed in community health care settings.

The National Institute of Aging, founded in 1986, has brought together 24 major medical research centers in the Consortium to Establish a Registry for AD (CERAD). The consortium has developed an extensive battery for evaluating and diagnosing persons with the MCI and dementia stages of ADRD. The CERAD battery includes demographic data on subject and informant, clinical history and examinations, extensive neuropsychological exams, laboratory and imaging studies, and neuropathological studies. One of the subtests of this battery, the CERAD 10-word list (CWL), has been shown to be one of the more sensitive tests for detecting MCI.[14] The CWL consists of three immediate-recall trials of a 10-word list, followed by an interference task lasting several minutes, and then a delayed recall trial with or without a delayed-cued-recall trial. The CWL is usually scored by recording the number of words recalled in each of the four trials. A single cutoff score for the delayed-recall trial, with or without adjustment for demographic variables, is typically used to determine whether cognitive impairment exists. This approach, however, may ignore other important

information contained in the CWL. For example, the measurement of attention, working memory, learning, retention and serial position effects may be important in identifying MCI. The research summarized herein tests the hypothesis that additional information contained in the CWL can more accurately distinguish MCI from normal aging.

As mentioned, the delayed-recall score of the CWL is reported to be somewhat sensitive for detecting the earliest stages of ADRD and has been used by the National Institute of Aging CERAD centers for approximately 20 years.[15] The sensitivity of delayed recall is high because it measures entorhinal and hippocampal cortical function, where the earliest neuropathological changes in AD occur.[16] In detecting subtle entorhinal or hippocampal dysfunction, measuring encoding may be more important than retrieval because analysis of the "people and doors" test showed no difference in classification accuracy between delayed recall (which requires that a word be previously encoded to be retrieved) and delayed-recognition (which eliminates retrieval and simply measures whether the word was encoded).[17] Disorders such as cerebrovascular disease, depression and Lewy body disease, in which delayed recall is impaired, but delayed recognition is intact, indicate a dysfunction of retrieval that is presumably caused by disrupted connections to the entorhinal-hippocampal circuit without damage to the circuit itself.

Encoding occurs during the immediate-recall trials of the CWL, and its persistence is measured with delayed-recall and delayed-recognition tasks. Our results suggest that the immediate-recall trials have encoding and/or retrieval information that enhances the power of delayed-recall measures to detect MCI. The relatively higher sensitivity of the present study's results compared with other studies of normal vs. MCI is likely caused by the use of all of the encoding and retrieval measures in the CWL data, including weighting of each word's relative importance by its position in the list and by the trial in which it is recalled. The CA-weighted column scores of the CWL data measure the difficulty of encoding and retrieval for each word in each trial. A simple summation or cutoff score of the number of words recalled across the four trials would not account for such weightings of encoding and retrieval difficulty.

With approximately 95 percent of the MCI subjects having a diagnosis that would produce progressive decline, the high sensitivity in the study means that many non-AD diagnoses also show early changes in encoding and, or retrieval that differ from normal aging. The implication of an abnormal screening result based on the randomization validation method is that it is correct in about 94 percent of MCI cases, most of which are progressive, and incorrect (a false positive result) in about 11 percent of normal-aging subjects. The implication of a normal screening result is that it is correct in about 89 percent of all normal-aging subjects and incorrect (a false negative result) in approximately 6 percent of MCI cases. The probability that a person with a positive screening test result has MCI is 100 percent and the probability that a person with a negative screening test result is normal is at least 96.6 percent. These rather straightforward interpretations can provide guidance for busy clinicians as to whether to proceed with diagnosis and treatment.

Conclusions

CA can substantially improve the CWL, which has been internationally validated and is sensitive for detecting early stages of ADRD. Compared with the usual method of scoring and interpreting the CWL, the CA-weighted scores derived from the item responses increased sensitivity in detecting MCI by 12 percent while preserving high specificity. Following the literature search method for identifying normal vs. MCI studies, we found our results to be the highest reported. Because most other screening tests rely primarily on total scores that are not adjusted to maximize their explanation of the variance, they could be improved by incorporating the methods presented here. ❋

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Footnotes

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