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The use of informant-based questionnaires in differentiating mild cognitive impairment from normal aging

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The use of collateral information in characterizing cognitive and functional deficits is standard practice in both clinical and research settings when assessing individuals for mild cognitive impairment (MCI) and Alzheimer's disease (AD). This information is often combined with social history, family history and objective cognitive testing to assess a patient's current cognitive status. Since the advent of the Blessed Dementia Scale [1], several different informant-based instruments have been created and validated to assess cognitive status. Most of them have focused solely on differentiating individuals with clinical AD from those who are cognitively normal. However, the field of AD research and therapeutics is shifting toward a paradigm in which individuals are identified and diagnosed at much earlier stages of the disease [2]. This is underscored by the evolution of MCI as a diagnostic entity [3] into a therapeutic target [4]. As a result of these changes, there is a need for informant-based instruments that demonstrate good diagnostic accuracy when cognitive changes are more subtle and may be harder to detect.

Since AD prevalence is expected to increase in the USA [5], clinicians will be faced with the prospect of evaluating individuals for possible cognitive impairment. This issue may be further compounded by the possibility that screening for cognitive impairment may become mandatory under proposed healthcare reform [101]. These realities underscore the need for

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primary care and specialty clinicians to utilize brief and accurate cognitive assessments in their practices. In addition, preventative studies, which typically require several hundred participants, will also need to utilize instruments that are brief, accurate and can assess drug efficacy in an efficient manner.

> "The use of informant-based information can also be extremely helpful to clinicians when social and demographic factors impact cognitive and functional assessment."

The use of informant-based information can also be extremely helpful to clinicians when social and demographic factors impact cognitive and functional assessment. It is often the case that individuals who have high educational and occupational attainment may perform within normal limits on objective cognitive tests, but are clearly demonstrating cognitive and functional deficits as reported by spouses and other informants. This dichotomy of cognitive and functional status is not uncommon and presents a significant diagnostic challenge to clinicians. Informant-reported questionnaires are extremely useful to clinicians, as these instruments are less affected by cognitive reserve than objective cognitive tests.

The use of informant-based questionnaires also helps to alleviate problems associated with biases in self-reported cognitive function. Informants are often able to provide a more objective assessment of a patient's cognitive and functional status as patients themselves may attribute their deficits to age-related changes, lifestyle changes, stress and other factors. In some cases, patients may deny having any cognitive problems. Although the latter is often associated with clinical AD, anasagnosia can occur in MCI patients [6]. When a patient denies the presence of cognitive decline, informant-based information can help the clinician to glean a more accurate picture of a patient's cognitive status. Informant-based questionnaires, such as the AD8 [7], Informant Questionnaire on cognitive decline in the elderly (IQCODE) [8] and the Alzheimer's questionnaire (AQ) [9], have been developed to address these challenges.

> "The Alzheimer's questionnaire has demonstrated very good diagnostic accuracy for mild cognitive impairment with a sensitivity of 89% and a specificity of 91%."

The AD8 consists of eight items in which the informant indicates yes or no, if there has been significant change for that particular item. The eight items ask about changes in memory, functional ability and judgment/decision-making. The AD8 has demonstrated good diagnostic accuracy for differentiating individuals classified as having 'questionable dementia' from cognitively normal individuals on the Clinical Dementia Rating (area under the curve = 0.83) [10]. This classification is considered to be analogous to a diagnosis of MCI [11]. The reported sensitivity and specificity for the AD8 in differentiating questionable dementia from normal cognition is 74 and 86%, respectively [8].

The IQCODE appears in both long (26 items) and short form (16 items). The informant is asked to assess the degree of change for each item relative to the patient's status 10 years before assessment. The degree of change for each item is rated on a 1–5 scale with one signifying 'much improvement' and five signifying 'much worse'. The IQCODE addresses change in the areas of memory, functional ability and judgment/decision-making. However, there are also items that assess a patient's ability to learn new tasks. The IQCODE has shown equivocal results for detecting MCI with one study, yielding relatively good

sensitivity and specificity (82 and 71%), with an area under the curve value of 0.86 [12]. By contrast, Sikkes *et al.* found that the IQCODE was not able to accurately differentiate MCI from normal cognition [13].

The AQ is a relatively new informant-based questionnaire that consists of 21 items divided into five domains including memory, orientation, functional ability, visuospatial ability and language [14]. Items are posed in a yes/no format with the sum of points for 'yes' items equaling the total score that ranges from 0 to 27 with higher scores corresponding to greater impairment. Six items known to be predictive of a clinical AD diagnosis are weighted more heavily in the total score by being worth two points rather than one. The AQ has demonstrated very good diagnostic accuracy for MCI with a sensitivity of 89% and specificity of 91% [9]. A recent study of the AQ found that four items on the questionnaire accurately differentiated MCI patients from cognitively normal individuals [15]. Those four items included repetition of statements and questions in the same day, difficulty with orientation to time (day, date and others), difficulty with handling finances and visuospatial disorientation.

Although these instruments have shown good diagnostic accuracy for MCI, the recent focus on the use of diagnostic biomarkers such as cerebrospinal fluid $A\beta_{42}$ levels and amyloid imaging highlights the need to determine the combined diagnostic value of biomarker measures with informant-based questionnaires. A recent study by Galvin *et al.* found that the AD8 had good discriminatory power in identifying individuals who had positive cerebrospinal fluid $A\beta_{42}$ and amyloid imaging biomarkers [16]. These results suggest that data derived from informant-based instruments correlate well with AD-related pathology. Comparison with biomarkers has not been evaluated with the AQ or IQCODE. As clinical trials in MCI and AD increasingly utilize biomarkers and amyloid imaging in their protocols, informant-based questionnaires may be able to accurately assess drug efficacy in terms of associating neuropathological changes with clinical changes. One methodological aspect that is currently unknown is how well informant-based instruments predict longitudinal change and disease progression. Although cross-sectional studies are necessary to determine an instrument's diagnostic accuracy, longitudinal studies that assess an instrument's ability to detect conversion to MCI from normal cognition are needed.

> "The use of informant-based questionnaires in mild cognitive impairment will continue to plan an integral role in both clinical and research settings."

The use of informant-based questionnaires in MCI will continue to play an integral role in both clinical and research settings. For clinicians, these instruments provide semi-quantitative assessments of a patient's cognitive and functional status that can be used to supplement other historical, clinical and cognitive measures. The use of these instruments helps to avoid biases associated with self-reported cognitive status and better inform the clinician of a patient's cognitive status when the patient is unaware of their own deficits. Informant-based questionnaires are also valuable sources of data for clinical trials and observational studies. As the methodologies of MCI clinical trials and prevention studies continue to evolve, these studies will require instruments that are able to detect clinical changes that coincide with neuropathological changes. Given the new mandates for cognitive screening in older adults, informant-based questionnaires will enable primary care

physicians and other clinicians to quickly and accurately screen for incident cognitive decline. The use of informant-based questionnaires in the assessment of MCI will continue to provide tremendous value to both clinicians and researchers, and is becoming an increasingly important component of clinical diagnoses and clinical research.

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Biographies

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