Author's response to reviews

Title: Informant-Reported Cognitive Symptoms That Predict Amnestic Mild Cognitive Impairment

Authors:

Michael Malek-Ahmadi (michael.ahmadi@bannerhealth.com)
Kathryn Davis (kathryn.davis@bannerhealth.com)
Christine Belden (christine.belden@bannerhealth.com)
Sandra Jacobson (sandra.jacobson@bannerhealth.com)
Marwan N Sabbagh (marwan.sabbagh@bannerhealth.com)

Version: 4 Date: 3 August 2011

Author's response to reviews: see over
August 3, 2011

Dear Dr. Patel,

Enclosed are our point-by-point responses to the most recent comments sent by the reviewers for the article entitled “Informant-Reported Cognitive Symptoms That Predict Amnestic Mild Cognitive Impairment”. We have attempted to address each concern as thoroughly and accurately as possible and we hope that they are found to be satisfactory. Every effort has been made to conform to editorial parameters. All changes in the manuscript are highlighted in red.

All authors have contributed substantially to the manuscript, have read its final version, and agree with the presented findings. Mr. Malek-Ahmadi and Dr. Sabbagh take responsibility for the integrity of the data and the accuracy of the data analysis. We feel that this contribution is timely, current, and relevant to the literature. We look forward to a seeing it in press in the near future.

Sincerely,

Michael Malek-Ahmadi, MSPH
Marwan Sabbagh, MD, FAAN
Reviewer 1

Major point:
However, I still have some concerns regarding the interpretations of the results obtained in this study. I feel that the authors overstate the importance and clinical/diagnostic utility of their results from the regression analysis when they claim that “certain AQ items can differentiate individuals with aMCI from those experiencing age-associated changes in memory and cognition.” There is no question that there is an association of the four items and the group membership of the participants (cognitively normal or aMCI). However, the results of the regression analysis do not provide convincing evidence that these four items should be used diagnostically or as screening measures. The odds ratios in Table 3 are large, but, as the authors correctly acknowledge the CIs are very broad. In any case, there is no compelling evidence why someone should choose this questionnaire (and the specific four items) over the numerous brief questionnaires or measures that already exist.

An additional logistic regression model was carried out with only the 4 significant AQ items while correcting for age and education. This model was used to derive sensitivity, specificity, and AUC in order to demonstrate clinical validity. The following paragraph has been added to the Results section:

“In order to more accurately characterize the clinical validity of these findings, a second non-stepwise logistic regression analysis was carried out which used only the four significant AQ items while correcting for age and education. This model yielded a sensitivity of 80.30 (67.00, 89.53) and specificity of 81.80 (69.67, 90.37) with an area under the curve (AUC) value of 0.94 (0.89, 0.99).”

The following paragraphs have been added to the Discussion to address the why using the AQ is advantageous to other measures:

In addition, the ability of other widely-used informant-based instruments to accurately identify clinical aMCI has not been established. The validity and accuracy of the AD8 has been established in clinical AD and in individuals with a CDR global rating 0.5 which is considered “very mild dementia” [32]. It is important to note that this categorization (CDR = 0.5) does not necessarily equate to a clinical diagnosis of aMCI so it is uncertain whether the AD8 can accurately identify clinically-defined aMCI cases. In addition, a recent study demonstrated that the IQCODE does not have high sensitivity in the detection of aMCI [33]. As mentioned earlier, a previous pilot study of the AQ demonstrated high sensitivity and specificity for aMCI when compared to cognitively normal individuals. The results of the current study showed that four statistically significant AQ items accounted for large proportion of the variance between aMCI and CN individuals and also yielded high sensitivity and specificity in differentiating the two groups.
Overall, the results of this study indicate that certain AQ items can differentiate individuals with aMCI from those experiencing age-associated changes in memory and cognition. As assessed by the AQ, difficulties with orientation to time, repetition of questions and statements, difficulties in managing finances, and visuospatial disorientation were all significant predictors of aMCI as diagnosed by an expert in memory disorders.

Given that memory complaints are commonly reported by elderly patients and their family members [7], a means to quickly and accurately identify individuals who may be in the early stages of AD and in need of further evaluation is critical to not only cost containment and resource management, but also to earlier diagnosis in order to improve disease outcome. These data indicate that problems with orientation to time, repeating statements and questions, difficulty managing finances, and trouble with visuospatial orientation may accompany memory deficits in aMCI. From a clinical standpoint, these findings are important as it will allow clinicians to more easily and accurately determine which individuals require further assessment of cognitive problems.

Minor points:

1. It would be useful to include in Table 3 how much variance is accounted for by the four items.

The Nagelkerke $R^2$ measure was added to demonstrate the amount of variance accounted for in the stepwise logistic model which included the 4 AQ items. This is described in the Statistical Analysis and the Results sections. In addition, the limitations of this measure are described in the Discussion section.

Results

The resulting stepwise logistic model yielded a Nagelkerke $R^2$ of 0.71 indicating that a large proportion of the variance between aMCI and CN individuals was accounted for by the four AQ items.

Discussion

In addition, the $R^2$ value may not truly represent the amount of variance accounted for by the model. The reason for this is that $R^2$ values in logistic models are approximations of linear-based $R^2$ measures and are not fully equivalent. In addition, $R^2$ measures used in logistic models are prone to bias when used with small sample sizes and may result in an inflated estimate of the amount of variance accounted for.

2. The first two sentences of the Intro imply that MCI represents a dementing process. Though individuals with MCI are at higher risk for dementia, MCI is a clinical syndrome with multiple etiologies and outcomes that range from normal cognitive aging to dementia, so it does not always represent a dementing process.
The first sentence of the Introduction has been changed to:

“The process of differentiating age-associated memory decline from those who might have a clinically significant disorder of memory and cognition is difficult.”

The second sentence, “In particular, distinguishing individuals with amnestic mild cognitive impairment (aMCI) from those who are cognitively normal (CN) is challenging, as memory and cognitive complaints are often reported in both groups from both the patient and informants” has been retained in its original form in order to help bring focus to the main aim of the study (differentiating aMCI from Cog Norm).