Aging

Development and Validation of the Alzheimer's Questionnaire (AQ)

Michael Malek-Ahmadi*, Marwan N. Sabbagh

Banner Sun Health Research Institute, Cleo Roberts Center for Clinical Research, Sun City, AZ, USA

The Alzheimer's Questionnaire (AQ) was developed to be brief and accurate informant-based assessment for primary care and geriatric physicians to use in screening for cognitive impairment. To date, several studies have been carried out and published establishing the diagnostic accuracy and psychometric validity of the AQ. This paper will provide a review of the studies that have been carried out to establish the AQ as a valid and accurate informant-based assessment of cognitive function. *Journal of Nature and Science, 1(5):e104, 2015*

dementia assessment | informant-based assessment | cognitive decline, | Alzheimer's disease | mild cognitive impairment

The use of informant-based instruments in the assessment of cognitive decline has been an integral part of both clinical assessments and research studies for some time. Nowhere is the utility of these instruments more prescient than in the area of Alzheimer's disease (AD) where assessments of cognition and functional capacity are often carried out via an informant who is often the spouse, significant other, or child of the patient. Although informant-based instruments such as the AD8 [1] and IQCODE [2] have been used in this capacity for some time now, the recent shift toward accurately identifying and treating individuals in prodromal stage of AD has forced clinicians and researchers to begin utilizing instruments that are sensitive to the subtle, but significant changes in cognition present in prodromal AD.

The term mild cognitive impairment (MCI) has been synonymous with prodromal AD since its initial conceptualization [3] as it was intended to identify individuals at-risk for developing clinical AD. Subsequent efforts to refine MCI as a diagnostic entity resulted in the classifications of amnestic and non-amnestic MCI, which differentiate between those showing impairment in the domain of memory (amnestic) versus those who demonstrate impairment in non-memory domains [4]. More recent efforts to clarify the etiology of amnestic MCI have resulted in the classification of "MCI due to Alzheimer's disease" [5]. This classification has resulted in a more specific group of cognitively impaired individuals to be targeted and assessed for disease-modifying treatments. From a clinical standpoint, it also provides more clarity regarding the underlying etiology of cognitive impairment which often dictates a clinician's treatment plan for a patient. Currently, there are no therapies approved by the Food and Drug Administration for the treatment of prodromal AD and as a result treatment is not initiated until a patient presents with cognitive and functional impairment consistent with a clinical AD diagnosis.

Despite the increasing prevalence of AD in the United States [6], many cases often go undetected as geriatric clinicians are often faced with addressing multiple medical issues within a very short office visit. As a result, cognitive impairment often goes undetected until it is moderately advanced [7,8]. The Patient Protection and Affordable Care Act of 2010 has specific mandates for disease screening for Medicare recipients, among these is a mandate for the screening of cognitive impairment [9]. Given these demands, there is a significant need for a brief and accurate screening tool that can be easily implemented in primary care settings [10].

The Alzheimer's Questionnaire (AQ)

The AQ was developed to be a tool that primary care clinicians can use to quickly and accurately screen for cognitive impairment due to AD. The AQ is an informant-based assessment consisting of 21 yes/no questions that can be administered in approximately three minutes. The individual items on the AQ are divided into the domains of Memory, Orientation, Functional Ability, Visuospatial, and Language. Items that receive a 'yes' response are given one point, however six items known to be associated with clinical AD are given more weight and are worth two points. The total AQ score ranges from 0 to 27 with higher scores indicating greater impairment.

The initial pilot study of the AQ [11] found that the instrument has excellent sensitivity (87%) and specificity (94%) for aMCI and AD (sensitivity = 99%, specificity = 96%). The AQ also demonstrated good internal consistency (Cronbach's $\alpha = 0.88$). This pilot study was then followed by a larger validation study that included 300 individuals (100 AD, 100 aMCI, 100 Normal) [12]. The results of the validation study were very similar to that of the pilot study with sensitivity and specificity for aMCI being 89% and 91%, respectively. Internal consistency remained high (Cronbach's $\alpha = 0.89$) while the between-domain correlations were modest ($r = 0.45 – 0.69$) indicating that the individual domains of the AQ are measuring distinct constructs.

Further Analysis of the AQ in aMCI

The results of the pilot and validation studies described above prompted a more detailed exploration of the AQ's performance in differentiating aMCI from normal cognition. Using a subset of aMCI and cognitively normal individuals from the validation study, analyses of the individual AQ items were carried out to determine which cognitive symptoms were most strongly associated with aMCI [13]. Four AQ items were strong indicators of aMCI which included: repetition of statements and/or questions [OR 13.20 (3.02, 57.66)]; trouble knowing the day, date, month, year, and time [OR 17.97 (2.63, 122.77)]; difficulty managing finances [OR 11.60 (2.10, 63.99)]; and decreased sense of direction [OR 5.84 (1.09, 31.30)]. These four items accounted for approximately 71% of the variance between aMCI and cognitively normal individuals after controlling for age and education.

More recent work by Salazar and colleagues [14] found that the AQ was able to accurately differentiate aMCI from normal cognition in a sample of Hispanic individuals. Results of this study also found that the AQ was not significantly associated with gender, education or language (English vs. Spanish), but did show a significant association with age. When used as a predictor of the Clinical Dementia Rating Sum of Boxes, the AQ explained 9% of the variance in this measure independently of age, education, gender, and language. Furthermore, Salazar and colleagues found that the AQ "may have a bias in favor of detecting amnestic MCI cases…" and that its predisposition toward memory items may increase its ability to accurately identify pre-clinical AD cases.

The findings of these studies are important given that AD researchers and clinical trialists are shifting to a paradigm where individuals are targeted for treatment at increasingly earlier stages of the disease. Ultimately this will shift clinicians' focus on cognitive assessment in older adults so that individuals are identified more accurately in earlier stages of the disease course where disease-modifying treatments will have the greatest chance of providing optimal therapeutic outcomes.

Conflict of interest: No conflicts declared.

*Corresponding Author: Michael Malek-Ahmadi, MSPH. The Cleo Roberts Center for Clinical Research, Banner Sun Health Research Institute, 10515 West Santa Fe Drive, Sun City, AZ 85351
Telephone (623) 832-6500; Fax (623) 832-6504
E-mail: michael.ahmadi@bannerhealth.com

Correlation of AQ to Cognitive and Functional Measures

Further studies of the AQ have been carried out to determine the extent to which it correlates to commonly-used cognitive screening and functional measures. Since the Mini Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA) are two of the most commonly-used objective cognitive tests, determining the extent to which the AQ correlates to these measures is important in order to corroborate informant-reported cognitive changes with objective, performance-based cognitive tests. Malek-Ahmadi et al [13] found that the AQ correlates moderately with the MMSE ($r = -0.56$) and MoCA ($r = -0.46$). This study also used compared the AQ with the Clinical Dementia Rating Sum of Boxes (CDR-SOB) and found a strong correlation ($r = 0.79$). Since the CDR-SOB encompasses a wide variety domains (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies) and is often used as the primary outcome in clinical trials and observational studies, demonstrating a strong correlation provides further validity to the AQ in its ability to accurately assess cognitive decline associated aMCI and AD.

A more recent study carried out by Budolfson et al [16] investigated how well the AQ correlates with traditional neuropsychological measures used to make clinical diagnoses of aMCI and AD. Using a large age-, education-, and gender-matched group this study found that the AQ correlated strongly with the MMSE ($r = 0.71$) and the Dementia Rating Scale-2 (DRS-2, $r = 0.72$). The AQ demonstrated strong correlations with the Rey Auditory Verbal Learning Test (RAVLT) ($r = -0.61$) and the Brief Visuospatial Memory Test-Revised (BVMT-R) ($r = -0.65$). Moderate correlations between the AQ and measures of executive function were also found (Trails B, $r = 0.53$; Stroop Color/Word, $r = -0.51$). This study also found that the AQ provided significantly better diagnostic accuracy in identifying aMCI cases when combined with the MMSE than if the MMSE were used in isolation.

The findings of Budolfson et al [16] demonstrate that the AQ correlates well with established measures of memory and executive function, which is important given that these domains are the ones in which decline is most often noted in aMCI cases. The additional diagnostic value that the AQ provides to the MMSE is also important given that many clinicians still utilize the MMSE in screening for cognitive decline. This finding suggests that more accurate identification of cognitively impaired individuals may be possible when the AQ is used in conjunction with the MMSE.

Longitudinal Assessment of Change with the AQ

Malek-Ahmadi et al [17] assessed the ability of the AQ to measure 1-year changes in cognition in aMCI, AD, and cognitively normal individuals. This study first assessed the sensitivity to change of the AQ in comparison to the MMSE and the Functional Activities Questionnaire (FAQ). Within the aMCI group the AQ showed small sensitivity to change ($d = 0.27$) as did the FAQ ($d = 0.30$) and MMSE ($d = 0.22$). Small sensitivity to change was also noted in the AD group for the AQ ($d = 0.37$). However, hypothetical clinical trial sample size calculations found that the AQ would require substantially fewer subjects per treatment arm when compared to the MMSE indicating that the AQ demonstrates greater sensitivity to change than the MMSE. The AQ was also found to be a significant predictor of decline as measured by the changes in CDR Global Score (OR = 1.20, 95% CI: 1.09, 1.32; $p<0.001$).

Reliable change index (RCI) analysis found that the AQ identified clinically significant change among aMCI cases at a greater rate (24%) than the FAQ and MMSE (both 17%). The results of the RCI analysis demonstrate that the AQ goes beyond demonstrating statistically significant differences as these results show that the AQ is sensitive to clinically significant change in a group of individuals considered to be at risk for developing AD.

Conclusion

To date, several studies have demonstrated the diagnostic accuracy and psychometric validity of the AQ. As an informant-based instrument for assessing cognitive decline, the AQ has shown that it can accurately differentiate both aMCI and AD when compared to cognitively normal individuals [11,12]. The pilot study of the AQ [11] yielded very favorable diagnostic ability for both aMCI (AUC = 0.95) and AD (AUC = 0.99). These results were replicated in a larger sample of aMCI, AD, and cognitively normal individuals [12]. Further studies have shown that it correlates well with other established measures of cognition and function while at the same time showing reasonable sensitivity to longitudinal change in aMCI and AD cases [16,17]. The utility of the AQ has been further supported by its translation into Spanish and its adoption by the by British Columbia Ministry of Health as a recommended assessment for cognitive impairment in older adults [18]. In addition, the AQ was recently added to the American Psychological Association's PsycTESTS® database [19].

Despite the number of studies that have been completed on the validation of the AQ, other areas of validation are still needed. Some important psychometric aspects that have yet to be addressed are that of inter-rater agreement and intra-rater reliability. Determining if the AQ provides accurate assessments across a spectrum of clinicians will be important in demonstrating its utility in the different settings in which older adults are assessed for cognitive decline. Another important area of study for the AQ will be to determine how well it correlates to biomarkers of AD pathology. As both cerebrospinal fluid and brain imaging markers become more prevalent in AD research studies and clinical settings, determining the extent to which the AQ correlates with these markers will be important as this would demonstrate the AQ's ability to measure cognitive and functional change associated with the pathological change. In addition, studies demonstrating the AQ's correlation with AD neuropathology and AD-specific biomarkers have not been carried out. Given that up 20% of clinically-defined AD cases may not have evidence of beta-amyloid [20], correlating the AQ with known AD biomarkers is needed. Also, the extent to which the AQ can predict conversion from normal cognition to aMCI and aMCI to AD has not been assessed nor has its sensitivity to treatment response been evaluated. All of these areas will be necessary to investigate in order to fully validate the AQ as an instrument specific to the detection of clinical AD.

Acknowledgements

Supported by the Banner Sun Health Research Institute, NIA P30 AG 019610, ADHS AGR 2007-37, and the Arizona Alzheimer's Research Consortium.

1. Galvin JE, Roe CM, Xiong C, Morris JC (2006) Validity and reliability of the AD8 informant interview in dementia. Neurology, 67:1942-1948.
2. Jorm AF (2004) The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): A review. International Psychogeriatrics, 16(3):275-293.
3. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. Archives of Neurology, 56:303-308.
4. Petersen RC, Negash S (2008) Mild cognitive impairment: An Overview. CNS Spectrums, 13:46-53.
5. Albert MS, DeKosky ST, Dickson D, *et al* (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers and Dementia, 7:270-279.
6. Alzheimer's Association (2014) Alzheimer's Disease Facts and Figures 2014. Accessed electronically at http://www.alz.org/alzheimers_disease_21590.asp on 2/13/15.
7. Larson EB (1987) Recognition of dementia: discovering the silent epidemic. Journal of the American Geriatrics Society, 46:1576-1577.
8. Valcour VG, Masaki, KH, Curb JD, Blanchette PL (2000) The detection of dementia in the primary care setting. Archives of Internal Medicine, 160:2964-2968.
9. Your Guide to Medicare's Preventative Services. http://www.medicare.gov/Pubs/pdf/10110.pdf. Accessed on April 3, 2015.

10. Ashford JW, Borson S, O'Hara R, Dash P, Frank, L, Robert P, Shankle WR, Tierney MC, Brodaty H, Schmitt FA, Kraemer HC, Buschke H (2006) Should older adults be screened for dementia? Alzheimers and Dementia, 2:76-85.
11. Sabbagh MN, Malek-Ahmadi M, Kataria R, Belden CM, Connor DJ, Pearson C, Jacobson S, Davis K, Yaari R, Singh U (2010) The Alzheimer's Questionnaire: A proof of concept study for a new informant-based dementia assessment. Journal of Alzheimer's Disease, 22(3):1015-1021.
12. Malek-Ahmadi M, Davis K, Belden CM, Laizure B, Jacobson SA, Yaari R, Singh U, Sabbagh MN (2012) Validation and diagnostic accuracy of the Alzheimer's Questionnaire (AQ). Age and Ageing, 41(3):396-399.
13. Malek-Ahmadi M, Davis K, Belden CM, Jacobson SA, Sabbagh MN (2012) Informant-reported cognitive symptoms that predict amnestic mild cognitive impairment. BMC Geriatrics, 12:3.
14. Salazar R, Velez CE, Royall DR (2014) Telephone screening for mild cognitive impairment in Hispanics using the Alzheimer's Questionnaire. Experimental Aging Research, 40:129-139.
15. Malek-Ahmadi M, Davis K, Belden C, Sabbagh MN (2014) Comparative analysis of the Alzheimer's Questionnaire (AQ) with the CDR Sum of Boxes, MoCA, and MMSE. Alzheimer's Disease and Associated Disorders, 28(3):296-298.
16. Budolfson K, Malek-Ahmadi M, Belden C, Powell J, Davis K, Jacobson SA, Sabbagh MN (2015) Neuropsychological Correlates of the Alzheimer's Questionnaire (AQ). *Journal of Alzheimer's Disease*, DOI 10.1323/JAD-142388.
17. Malek-Ahmadi M, Chen K, Davis K, Belden CM, Powell J, Jacobson SA, Sabbagh MN(2015) Sensitivity to change and prediction of global change for the Alzheimer's Questionnaire. Alzheimer's Research & Therapy, 7:1.
18. British Columbia Ministry of Health: Practice Guidelines: Cognitive Impairment: Recognition, Diagnosis and Management in Primary Care http://www2.gov.bc.ca/gov/topic.page?id=45355C78707542F5BB248E74C17CE623. Accessed on April 3, 2015.
19. American Psychological Association. http://www.apa.org/pubs/databases/psyctests/index.aspx?tab=1. Accessed on April 3, 2015.
20. Witte MM, Trzepacz P, Case M, Yu P, Hochstetler H, Quinlivan M, Sundell K, Henley D (2014) Association between clinical measures and florbetapir F18 PET neuroimaging in mild or moderate Alzheimer's disease dementia. Journal of Neuropsychiatry and Clinical Neurosciences, 26:214-220.