Journal of Alzheimer's Disease 5 (2003) 391–398
IOS Press

Designing a Brief Alzheimer Screen (BAS)

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Abstract. *Context* With advances in the treatment of Alzheimer's disease (AD), clinical focus has shifted to early patient identification. Memory recall tests and category fluency distinguish normal individuals from early AD patients.
Objective Develop a brief test for general practitioners to screen for AD.
Design Examination of items from the MMSE and category fluency.
Setting and Participants A Brief Alzheimer Screen (BAS) was developed from cognitive assessments on 406 normal subjects and 342 mild AD patients in the CERAD (Consortium to Establish a Registry for AD) dataset. The derived measure was then applied to a second validation sample.
Main Outcome Measure Logistic regression was used to derive a predictive equation, which was then applied to two validation samples to estimate sensitivity and specificity.
Results The resulting logistic model for discriminating between mild AD and controls included: recall of 3 words, number of animals named in 30 seconds, date, and spelling of WORLD backwards, ($p < 0.001$ for each) accounting for 77% of the variance. When applied to the validation samples, sensitivity and specificity were over 99% and 87%, respectively.
Conclusions These data support the use of the BAS as a potential screen of patients over 60 years of age.

1. Introduction

In the last two decades, dementias in general and Alzheimer's disease (AD) in particular have become recognized as major causes of morbidity and mortality in the elderly. Clinically significant incidence of disease begins around 60 years of age and increases thereafter, approximately doubling every five years [4, 18,19]. Prevalence approximates 10% of those persons over 60 and may reach nearly 50% by age 85 [12]. Recent studies have suggested that mild cognitive impairment (MCI), impaired memory without significant daily living impairments, may represent an early phase of AD and may constitute an additional 10% to 15% of the population over the age of 60 [34,37,46]. As the age of the world population increases in the next 50 years, the prevalence of AD is expected to increase substantially [4] and consume a large portion of medical and financial resources. Recent studies have also suggested that cholinesterase inhibitors and antioxidants may slow the progression of AD and substantially improve its outcome [21,41,44]. These data provide considerable promise for the delay and prevention of AD and for slowing its course in the early phases. This may be realized in the near future with pharmaceutical agents currently under development [16,48]. Given the advances in diagnosis and treatment of AD, it appears that it is becoming increasingly important to identify patients with the earliest indications of disease [10,34].

One clinical problem for the practicing physician is distinguishing individuals with mild dementia from normal elderly persons. Recognition of dementia is a

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ISSN 1387-2877/03/$8.00

serious difficulty for medical practitioners [15]. When a clinician approaches a patient who may have cognitive impairment, the most useful source of information about the patient's difficulties is classically considered to be the history of the development of memory difficulties [2]. Clinicians rely on the report of an individual who knows the patient well [34]. Early AD patients have memory problems [40], and some do complain of memory loss [17]. But, many AD patients have little insight into the severity of their own failing memories [23] and may not report these symptoms to their physicians [42], leading to an under-detection of AD in clinical settings [6]. A routine screening test of cognitive function (that could be quickly and easily administered in the medical office setting) would help to identify patients with mild dementia and who should have further examination. Such a screening has been recommended [39,50], but it is not currently part of the American Academy of Neurology (AAN) guidelines [22]. However, clinical usefulness suggests the need for screening especially in persons with risk factors for AD [39,50] and diagnostic criteria for AD incorporate an objective evaluation of cognition [31].

The need for short screening instruments for AD has been widely recognized and several have been developed. Nevertheless, screening instruments are rarely used in general clinical practice, and careful analysis has led to a recommendation that currently available screening tools are not adequate to use in routine clinical practice [29,38]. The Mini-Mental State Exam (MMSE) [14], which usually takes 10–15 minutes to administer, is the only test that seems to be used by some general practitioners. It can be a long screening test and has been more useful in assessing dementia severity than as a screening tool [2,9,24,25,54]. The "clock drawing" task has been widely advocated, in spite of its low sensitivity and specificity [28,49,52], but it is not used in routine clinical geriatric practice. Other screening tests have been proposed, but either because they take too long, or they are too cumbersome to administer, none are widely used by general practitioners. The recently proposed "7 minute screen" [51], which contains recall items, category fluency, and temporal orientation has good positive predictive value for memory problems but may still be too long for routine use in a busy geriatric practice. For a test to be acceptable for general routine screening, the administration time will probably have to be around 2 minutes.

Several studies have consistently shown that memory recall is the most sensitive indicator of early AD [5,20, 27,30,36,40], but standard learning and recall tests can be time consuming. A notable exception is the Memory Impairment Screen [5], a measure that provides an objective learning and recall assessment in a relatively brief interval. At the same time, evaluation of retrieval capabilities in the form of category verbal fluency tasks has successfully discriminated between demographically matched AD and normal older adults [7,32,33]. Given a clear need for a suitably short and adequately reliable screening test for use in clinical practice and the demonstrated classification capabilities of the MMSE and category verbal fluency tasks for AD, we explored components of these brief measures separately and in combination.

For the development of a screening test that has wide applicability, we chose to work with the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) [33] dataset. This dataset contains a compilation of mental status test results from both AD patients diagnosed with NINCDS-ADRDA criteria, modified to increase diagnostic stringency (requiring 12 months rather than 6 months duration of memory impairment and a gradual onset and progression of symptoms) and normal controls from a broad assortment of research centers across the US. While the individuals in this dataset are not fully representative of the population in this country (primarily for reasons including race and education), they do represent a large defined group with geographic diversity that is typical of many clinic populations. Further, these data were collected before the advent of treatment interventions for AD. This dataset contains a wide range of clinical and mental status items, therefore lending it to analytical approaches using item response theory for the statistical assessment of potentially useful indicators for early AD.

Data from prior studies [1–3,13,35,43] indicate that certain items of the MMSE have good discriminating power in the assessment of dementia severity early in the course of the progression. Other data [33] indicate that animal naming is particularly useful for discriminating between early AD patients and normals. Accordingly, we chose to focus on the MMSE and animal-naming tests from the CERAD dataset to identify a group of items that best discriminates mild AD patients from normal older adults.

We then evaluated the resulting screening items in mild AD patients and in patients diagnosed as non-demented at the Memory Disorders Clinic and a large normal control population [46] at the University of Kentucky Alzheimer's Disease Research Center (ADRC).

Table 1
Characteristics of UKADRC datasets

	Mild AD	Non-demented clinic patients	Normal Controls
N	503	70	657
White (%)	98.4	98.6	98.9
Age (mean ±SD)	62.1 ± 10.4	76.7 ± 7.8	73.1 ± 8.2
Male (%)	28.4	45.7	36.6
Education (mean ±SD)	12.9 ±3.7	12.2 ±3.7	15.8 ±2.5

2. Materials and methods

2.1. Populations

The CERAD data set was chosen for developmental analysis because it carefully defined a population of AD patients and cognitively intact controls evaluated by experts at ADRCs around the United States. Subjects were enrolled between 1989 and 1995. This data set has been extensively described in several papers [8, 33,57] and is available on CD-ROM. In this analysis we included the "entry visit" data for controls and AD patients whose MMSE score and category fluency (animal naming) were recorded.

The mild AD CERAD group consisted of the 342 patients with a diagnosis of probable AD [31] at all visits and an entry MMSE score of at least 20 (mean MMSE score of 22.6 ± 2.0). Note that the MMSE score was used only to exclude the more severely demented patients and was not used for estimating severity otherwise. In this group there were 298 (87%) whites and 139 (41%) males. The mean (±SD) age was 72.8 ± 7.7 years and the mean (±SD) education 13.4 ± 5.8 years. The CERAD control group consisted of the 406 normal individuals without a dementia diagnosis at all visits (1 to 6 years after entry), an entry MMSE score greater than 25 (mean MMSE score 28.9 ± 1.1), and no other neurological conditions. Based on these criteria 10 individuals were excluded (all of them had MMSE 25 or below, 2 had other neurological problems). Given the current concept of Mild Cognitive Impairment (MCI) and the era during which the CERAD data were collected, the remaining 8 'controls' without coexisting neurological diagnoses may have represented MCI cases. Without long-term follow up of these individuals, we can only speculate as to why their MMSE scores were so low. However, this exclusion was not considered to be of adequate relevance to bias the analysis, although inclusion of these cases would have reduced the sensitivity and specificity values slightly. In this group there were 380 (94%) whites and 136 (34%) males. The mean (±SD) age was 68.6 ± 7.9 years and mean (±SD) education 13.8 ± 3.1 years.

The UK-ADRC data set consisted of three groups, 503 patients with mild AD (probable or possible AD at all visits, CDR score of 0.5 or 1, MMSE and category fluency recorded) who were diagnosed in the UK-ADRC Memory Clinic, a non-demented group (Memory Clinic referrals), with 70 "non-demented" patients (no MCI or dementia diagnosis, MMSE and category fluency recorded), and 658 control subjects from the BRAiNS study of elderly volunteers from the community who are evaluated each year and donate their brain for autopsy after death [11,47]. The race, age, sex, and education characteristics for these three groups are shown in Table 1.

2.2. Statistical analyses

2.2.1. SAS was used for statistical calculations [45]

First, animal naming in the CERAD dataset was examined for the AD and control groups with respect to the number of animals named in multiples of 15 seconds (eg. 15, 30, 45, and 60 seconds) using receiver-operator characteristic (ROC) analysis [7,24]. The ROC – Area Under the Curve (AUC) of 15, 30, 45, 60 seconds were derived. Since our goal was to design a brief screening tool and these results suggested that animals named in 30 seconds (AUC = 0.83) provided substantially more information than animals named in 15 seconds (AUC = 0.74) and nearly as much information as did 45 (AUC = 0.86) or 60 (AUC = 0.97) seconds, naming of animals in 30 seconds was therefore chosen as a variable of interest. Note that these AUC values compare well to those provided by Chen et al. [7] for this measure of category fluency (AUC = 0.77).

The CERAD data were randomly divided into two subgroups of equal size: the derivation and validation subgroups. A backward logistic regression analysis predicting group membership (normal or AD) was performed on the derivation group's data using all of the MMSE items and Animal30 score. The resulting items were then used in combination to develop the Brief Alzheimer's Screen (BAS) to distinguish AD patients from control individuals. The BAS was subsequently evaluated in the CERAD validation subgroup and then

Table 2
Responses (mean ± SD or percent) to the BAS items for the Mild AD and control groups and their beta coefficients

Item		Mild AD	Control	Standardized beta-coefficent
Recall	0	55	0	2.09
	1	27	7	
	2	15	29	
	3	4	71	
Animals		7.5 ± 2.8	12.5 ± 3.2	1.41
Date		31	95	1.25
Spell	1	2	0	0.88
	2	4	0	
	3	9	3	
	4	20	5	
	5	64	92	

applied to the UK-ADRC data to determine the strength of its ability to discriminate patients from controls in an unrelated population. The ROC curve of the BAS was also compared to that of the MMSE.

3. Results

The backward logistic regression analysis of the derivation dataset identified the following four items starting with the most discriminating: The four most significant items ($p < 0.001$) were: Recall of the three items ("Apple, Table, Penny", R), Animal30 (A), Date ("What is the date", D), and Spelling 'World' backwards (S). The frequencies of correct responses for these items in the mild AD and control groups along with their standardized beta-coefficients from the logistic regression are presented in Table 2.

Using these coefficients as the weights, the optimal predictive model that differentiated the mild AD and control groups produced the following equation for the BAS:

$$\mathrm{BAS} = 3.03 \times \mathbf{R} + 0.67 \times \mathbf{A} + 4.75 \times \mathbf{D} + 2.01 \times \mathbf{S}$$

When we applied this equation to the validation group, the resulting group membership for the integer of the BAS (shown in Table 3) discriminated clinical cases from normal elderly quite well. If a cut-off BAS score of less or equal than 22 is used, the BAS produced 1% false positives and 10% false negatives, while a cut-off value of 26 produced 13% false positives and only 1% false negatives. The resulting group membership for the UK-ADRC validation sample is shown in Table 4. In this dataset, when using a BAS cut-off score of 26 the false negatives consisted of only 4% of the patients while the 2% of the controls were false positives.

Table 3
BAS scores for CERAD validation group

	BAS SCORE					
	3–22	23	24	25	26	27–39
Mild AD	90%	2%	1%	3%	3%	1%
Control	1%	2%	3%	2%	5%	87%

Table 4
BAS scores for UK-ADRC dataset

	BAS SCORE					
	3–22	23	24	25	26	27–39
Mild AD	92%	2%	1%	1%	2%	2%
Control	1%	1%	0.5%	0.5%	1%	96%

A comparison of the discriminability of the BAS and the MMSE, the ROC curves for both tests in the UK-ADRC data were compared and are presented in Fig. 1. AUC values were for the BAS and the MMSE 0.994 and 0.989 for Fig. 1a and 0.861 and 0.849 for Fig. 1b.

4. Discussion

Based on the results of our retrospective analysis of two existing data sets, we have constructed a theoretical screening test for AD that should be short and easy to use, and has high specificity to differentiate between mild AD and older adults with essentially normal mentation.

At the core of the BAS are components from the MMSE that have been demonstrated to be most effective for distinguishing between mild levels of dementia [1,2,13,35]. A category fluency test (animal naming), restricted to the first 30 seconds, adds further power to the discrimination. Together, these items should require less than 3 minutes to administer to an elderly patient.

In the application of the BAS, a cut-off score of 26 results in reasonable sensitivity and specificity for the

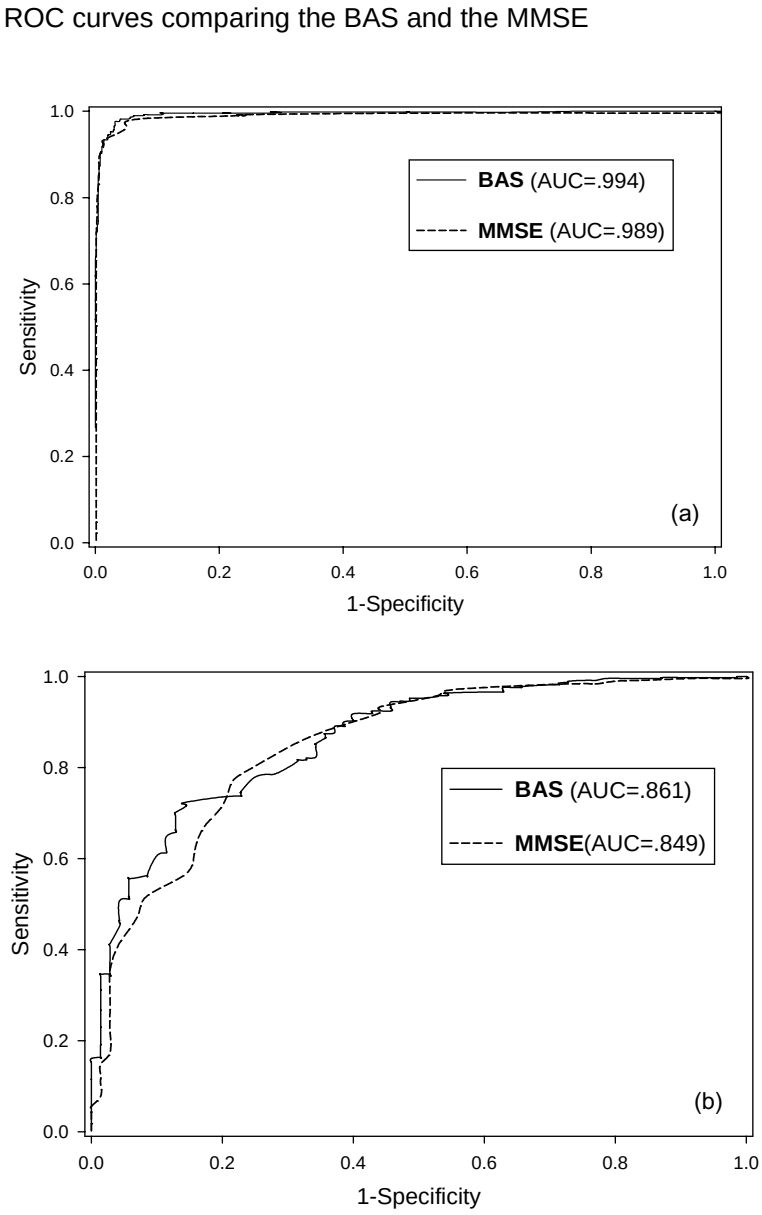

Fig. 1. a: UKADRC dataset, Mild AD versus control groups. 1b: UKADRC dataset, Mild AD versus non-demented patients groups.

diagnosis of AD, noticing that those patients that score between 23 and 26 need further cognitive testing to decide which category they fall into. It should be noted that the characteristics of mild AD patients and controls in the CERAD dataset might not be representative of the distribution of older patients in a general medical practice where base rates of AD may be lower. Further, a screening measure based on theoretical design may not perform as expected in a real clinical setting. Also, both datasets used in the development of the BAS contain a predominantly English speaking, highly educated, white population. Other studies have shown the effects of ethnicity on mental status performance e.g. [55,57]. In the CERAD data set the effects of ethnicity could not be readily evaluated on the BAS due to the small proportion of African-Americans in the control groups (6%) and no difference was found for the BAS in mild AD patients. Therefore care should be used when using the BAS in other populations. Additionally, the performance of this screening test cannot

be estimated for patients with other types of dementia or other neurological conditions such as Parkinson's disease. Therefore the predictive value of this screening measure needs to be evaluated in other settings and across different populations. However, AD constitutes approximately 2/3 of the population of dementia patients, and this test should detect close to 99% of these patients in the mild stage of this disease. Other causes of dementia might not affect performance in some unusual circumstances, but generally, most patients with cognitive dysfunction should at least be identified by this test as needing further assessment.

Data from larger epidemiological cohorts provide insights into other potential screening measures. The Mini-Cog [3] uses the MMSE's 3-item recall task with clock drawing as a screening for 'impairment' without a specific goal of differentiating normal aging from AD. Data from the MoVIES cohort using logistic analysis of scores (not items) from a larger test battery (that overlaps with CERAD) provides evidence that list learning and Trailmaking performances fare better than the MMSE in differentiating AD from normal aging. The BAS is a compromise between these approaches. Finally, as has been discussed by Kraemer [26], population selection can influence the results of any screening measure when the base rate of AD is small.

The BAS is not designed to detect or evaluate MCI, which is now considered by some investigators to be a precursor to AD [34]. Further prospective studies using this measure or similar measures with MCI subjects are needed to assess their efficacy in identifying this population that does not yet meet criteria for an AD diagnosis.

It is also important to remember that screening tests should not be considered diagnostic. They have significant false positive and false negative rates. Some patients, because of high education or other skills, perform well on any screen despite their affliction with early AD. Other non-demented patients, because of poor education or other non-organic deficits, may fail the screen. Of particular importance is the issue of education, which is known to affect performance on spelling "WORLD" backwards [53]. Low education and illiteracy may interfere with the application of this task and additional issues related to screening approaches still need to be considered. Factors such as gender, age, cultural background, language, or medical problems may influence the results of this or any screening test and should be evaluated in larger studies.

Acknowledgements

This research was supported in part by National Institutes of Health Grant 5-P50-AG05144 and the Department of Veterans Affairs.

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