INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2006; **21**: 239–245.
Published online 13 February 2006 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1450

Validation of the Spanish version of the Addenbrooke's Cognitive Examination in a rural community in Spain

A. García-Caballero[1]*, I. García-Lado[1], J. González-Hermida[1], MJ. Recimil[1], R. Area[2], F. Manes[3], S. Lamas[1] and GE. Berrios[4]

[1]*Servicio de Psiquiatría, Complexo Hospitalario de Ourense, Spain*
[2]*Servicio de Psiquiatría, Complexo Hospitalario Xeral-Calde, Lugo, Spain*
[3]*Departamento de Neurología, Instituto de Investigaciones Neurológicas Raúl Carrea -FLENI- Buenos Aires, Argentina*
[4]*Department of Neuropsychiatry, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK*

SUMMARY

Background The Addenbrooke's Cognitive Examination (ACE) is a brief cognitive test battery designed to detect and differentiate Alzheimer's disease (AD) and frontotemporal dementia (FTD). Translations of this instrument into French and Malayalam have been recently published.
Objective To adapt and validate the ACE into Spanish in a rural population of low-educational level.
Subjects A clinical group, composed of 70 patients affected by dementia and 25 patients with memory complaints without dementia, was compared with 72 controls matched for gender, age and educational level.
Method The clinical group was studied with standard neuropsychological instruments, all patients underwent neuroimaging [Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI), and Single Photon Emission Tomography (SPECT) in all cases of suspected FTD], as well as routine neurological examination. Both groups were studied with the ACE and Clinical Dementia Rating scale (CDR). Sensitivity, specificity, area under curve, reliability and Verbal-Language/Orientation-Memory (VLOM) ratio were calculated. Subsequently, the sample was stratified regarding educational level in two groups. Receiver Operating Characteristics (ROC) curves were calculated for these conditions. Different cut-off points were calculated addressing educational level.
Results ROC curves demonstrated the superiority of the ACE in the sub sample of patients that finished school at over 14 years old. VLOM ratio confirmed its usefulness for differential diagnosis between AD and FTD.
Conclusion The Spanish version of the ACE is a useful instrument for dementia diagnosis. In our sample VLOM ratio results were useful for differential diagnosis between AD and FTD. Different cut-off points must be used for different educational levels.

KEY WORDS — Addenbrooke's; ACE; Frontotemporal dementia; Alzheimer's disease; cognitive evaluation; education; Spanish

INTRODUCTION

Early detection of dementia is an important challenge for the physician, especially after the introduction of disease-modifying treatments.

Brief instruments such as the widely used Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975) have a poor sensitivity in early stages of dementia, especially when amnesia is the most prominent feature (Tombaugh and McIntyre, 1992) and they are not useful for detection of frontal symptoms (Gregory *et al.*, 1997).

On the other hand, comprehensive batteries such as CAMCOG (Huppert *et al.*, 1995) require specialized personnel and are beyond the scope of a bed-side test. In clinical practice this paradox has been solved by adding subtests to the MMSE, a strategy followed in

*Correspondence to: Dr. A. García-Caballero, Servicio de Psiquiatría, Complexo Hospitalario de Ourense. R/Ramón Puga no. 54, 32005, Ourense, Spain. Tel: 988-218990. Fax: 988-218991.
E-mail: Alejandro.Garcia.Caballero@sergas.es

Contract/grant sponsor: Dirección Xeral de Investigación e Desenvolvemento, Xunta de Galicia; contract/grant number: PGIDIT 03SAN 92302.

Received 1 March 2005
Accepted 18 August 2005

the literature with the validation of the so-called 'midi-batteries' (Tombaugh and McIntyre, 1992).

Bearing these factors in mind, a team led by JR Hodges and GE Berrios (Mathuranath *et al.*, 2000) designed the Addenbrooke's Cognitive Examination (ACE) a midi-battery that incorporates the MMSE, expanding memory, language, and visuospatial components and adding tests of verbal fluency.

The ACE has been translated into Malayalam and French (Mathuranath *et al.*, 2004; Bier *et al.*, 2005) and two teams have done a parallel adaptation into Spanish, in communities with different cultural features in Europe and America (Sarasola *et al.*, 2004).

Differences in neuropsychological performance regarding social factors and educational level have been demonstrated in different communities (Jagger *et al.*, 1992; Fisk *et al.*, 1995; Ostrosky *et al.*, 1998; Wackerbarth *et al.*, 2001), and extensively studied in populations similar to our sample in Portugal (Castro-Caldas *et al.*, 1998; Reis *et al.*, 2003) and Spain (Blesa *et al.*, 2001).The aim of our work was to adapt and validate the ACE in Spanish in a rural community of low-educational level in Galicia in the north-west of Spain.

METHOD

Adaptation

The ACE was translated into Spanish with adaptations concerning name and address-learning and delayed recall, semantic memory, word and sentence repetition and reading tests. The MMSE was substituted by its most widely used Spanish counterpart. Adaptation and psychometric properties of this instrument have been discussed elsewhere (Lobo *et al.*, 1999). Overlapped pentagons were conserved in their original angle for comparison purposes with international counterparts (Mathuranath *et al.*, 2000).

Name and address adaptation did not alter the number of items to remember in the task. In semantic memory, public figures were substituted by their Spanish counterparts. The name of the president of the United States was substituted by the name of the Pope, considered more ecological in a rural community of low educational profile in a catholic country such as Spain. Word repetition was adapted on phonetic grounds keeping a comparable difficulty for exploring aphasia between languages (number of diphthongs and consonant groups). Finally, adaptation of the lecture of irregular words was possible using a selection of words extracted from the Word Accentuation Test (Del Ser *et al.*, 1997). We think this strategy could be useful in other languages where reading irregularities are not frequent.

At different points of this process, members of the original team and Spanish speakers, suggested modifications. A pilot study of 20 cases was performed and modifications regarding name and address were required.

Participants

Following the design of the original study, two groups were considered. A clinical group of 70 dementia patients focused on initial stages ($\leq$CDR 1), was recruited from different outpatient settings together with 25 patients with memory complaints who did not fulfil DSM-IV criteria for dementia (APA, 1994). This clinic group was compared with 72 controls matched for gender, age and education.

Evaluation

All participants in the clinical group were studied with standard neuropsychological instruments [Spanish version of the MMSE (Lobo *et al.*, 1999), clock test, verbal fluency, word list learning and recall, Trail-Making Test (Reitan, 1971), and specialized tasks for frontal lobe pathology (when clinically required): Stroop test (Stroop, 1935) and/or Wisconsin Card Sorting Test (Nelson, 1976)]. All patients were subjected to a clinical, radiological (CT or MRI, and SPECT in cases of suspected FTD) and laboratory examination. Patients were classified into demented and non-demented groups, according to DSM-IV criteria (APA, 1994). The diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association criteria (McKhann *et al.*, 1984) and Vascular Dementia (VaD) on National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (Roman *et al.*, 1993). Patients diagnosed with FTD dementia conformed to the consensus criteria (Neary *et al.*, 1998). The diagnosis of Dementia with Lewy Bodies (DLB) was based on consensus guidelines (McKeith *et al.*, 1996).

The clinical group and control group were studied with the ACE and Clinical Dementia Rating Scale (CDR) (Hughes *et al.*, 1982).

Data analysis

SPSS 10 statistical software was used. Sensitivity, specificity, and cut-off point were calculated using

Table 1. Comparison of control, dementia and non dementia groups on demographics and ACE and MMSE mean (SD) scores in the complete sample

	Clinic group			*p* Value for D vs:	
	Dementia ($n=70$)	Non dementia ($n=25$)	Control ($n=72$)	ND	Control
Female sex (%)*	38 (54.3)	17 (68)	42 (58.3)		
Age, years**	74.19 (5.54)	74.64 (5.57)	72.58 (5.99)		
Education (years at finishing school)***	13.13 (2.36)	12.96 (2.09)	13.36 (2.98)		
MMSE (30)	20.10 (4.25)	25.48 (2.57)	28.04 (1.46)	****	****
ACE (100)	51.87 (11.73)	67.68 (6.87)	83.51 (7.39)	****	****

*Pearson Chi-Square $p=0.490$, **Kruskal-Wallis Test $p=0.165$, ***Kruskal-Wallis Test $p=0.665$, ****Mann–Whitney *U* test, two-tailed $p<0.001$.

ROC curve. Reliability and VLOM ratio were obtained.

Subsequently, the sample was stratified in two subsamples regarding educational level (≥ 14 and <14 years old at finishing school). This measure was used due to the inability of most patients in the low educated group to ascertain the number of years of education received. ROC curves for the ACE and MMSE in these sub samples were calculated and compared.

RESULTS

Table 1 summarizes the socio-demographic characteristics and mean (SD) composite score on the ACE and MMSE for dementia, non dementia and control groups in the complete sample. There were no statistically significant differences between groups, in gender ($\chi^2=1.426$, $p=0.490$), age ($\chi^2=3.067$, $p=0.165$) nor education ($\chi^2=0.815$, $p=0.665$).

Diagnostic categories within the clinical group have been summarized in Table 2. Severity of dementia was assessed by the CDR scale. The majority of patients included in the clinical group (68.6%) presented a CDR ≤ 1 and 100% presented a CDR ≤ 2.

Within the complete sample an ACE cut-off score of 68/100 points represented a value two SDs below the mean composite score for the control group. Even though this cut-off score was lower than the original British one (83/100), the psychometric properties of the ACE remained remarkable: sensitivity 92%, specificity 86%, area under roc curve 0.957; but only slightly better than the MMSE with the standard cut-off point (<24) in the same population (sensitivity 82%, specificity 98%, area under roc curve (AUC) 0.944). Reliability of the ACE was measured in terms of internal consistency, using Cronbach's alpha coeficient. The Cronbach's alpha for the ACE was 0.8201 (>0.8 is considered excellent). A comparison of ROC curves of ACE and MMSE, calculated for the complete sample is shown in Figure 1.

Table 2. Diagnostic categories in the clinic group

Clinic group ($n=95$)			
Dementia	70	Non dementia	25
AD	52	MCI	13
FTD	9	Mood disorder	9
VaD	3	Subjective Mnestic Claim	3
DLB	5		
HAS	1		

AD = Alzheimer disease; FTD = Frontotemporal dementia; VaD = Vascular Dementia; DLB = Dementia with Lewy Bodies; HAS = Hakim Adams Syndrome; MCI = Mild Cognitive Impairment.

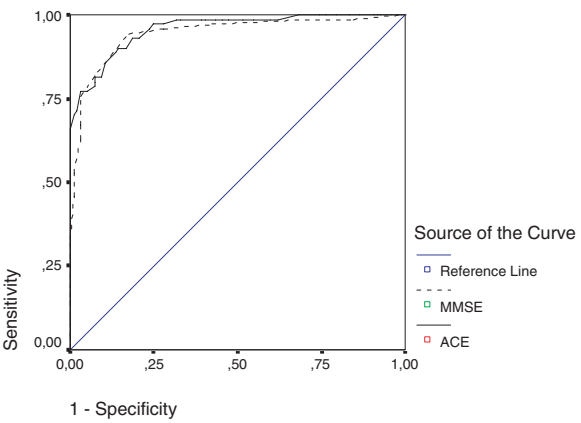

Figure 1. Comparison of ROC curves of ACE and MMSE in the complete sample

Table 3. Comparison of control, dementia and non dementia groups on demographics and ACE and MMSE mean (SD) scores in the stratified samples

	Clinic group						*p* Value for D vs:	
	Dementia		Non dementia		Control		ND	Control
	≥ 14 $n = 30$	< 14 $n = 40$	≥ 14 $n = 11$	< 14 $n = 14$	≥ 14 $n = 40$	< 14 $n = 32$		
Age, years*	73.40 (5.86)	74.78 (5.29)	72.23 (6.04)	75.43 (4.91)	70.97 (5.96)	74.59 (5.47)		
Education (age in years at finishing school)**	15 (2.39)	11.73 (0.96)	14.91 (1.30)	11.43 (1.02)	15.33 (2.34)	10.91 (1.49)		
MMSE (30)	21.03 (4.96)	19.40 (3.54)	26.00 (2.72)	25.07 (2.46)	28.40 (1.26)	27.59 (1.58)	***	***
ACE (100)	54.80 (13.14)	49.67 (10.19)	70.81 (7.20)	65.21 (5.68)	86.37 (5.83)	79.93 (7.64)	***	***

*Kruskal-Wallis Test $p > 0.170$, **Kruskal-Wallis Test $p > 0.05$.
***$p < 0.005$ (Mann–Whitney U test, two-tailed).

Our results also confirmed the usefulness of the Verbal-Language/Orientation-Memory ratio (VLOM) for differential diagnosis between AD and FTD dementia. In cases of Dementia with a CDR ≤ 1, a VLOM ratio > 2.80 correctly classified 91% of AD and conversely a VLOM ratio under 2.80 correctly classified 77% of FTD cases.

As we previously stated, in the second stage, the sample was stratified regarding educational level in two groups: $\geq$ 14years old ($n = 81$) and < 14 years old at finishing school ($n = 86$). There were no statistically significant differences between groups in each sub-sample, in age ([$\geq$ 14y.o] $\chi^2 = 3.427$, $p = 0.180$; [< 14] $\chi^2 = 0.241$, $p = 0.887$) nor education ([$\geq$ 14y.o] $\chi^2 = 2.007$, $p = 0.367$; [< 14y.o] $\chi^2 = 5.764$, $p = 0.056$).

Table 3 summarizes the socio-demographic characteristics and mean (SD) composite score on the ACE and MMSE for dementia, non dementia and control groups in the stratified samples.

ROC curves demonstrated the superiority of the ACE (AUC = 0.960) over the MMSE (AUC = 0.922) 0.922) in the higher-educational level sub sample (Fig. 2). Conversely, they demonstrated the absence of differences between these instruments in the lower-educational level sub sample ($AUC_{ACE} = 0.963$, $AUC_{MMSE} = 0.967$) (Fig. 3).

Within the low-educational sub sample a cut-off score two SDs below the mean of the control group ($\leq$ 65/100) obtained a sensitivity of 90% and a specificity of 83%. These results were similar to those obtained with the previously quoted cut-off score of

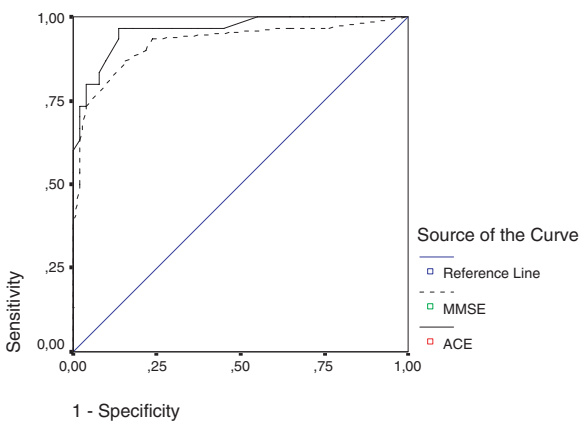

Figure 2. Comparison of ROC curves of ACE and MMSE in participants older than 14 years old at finishing school

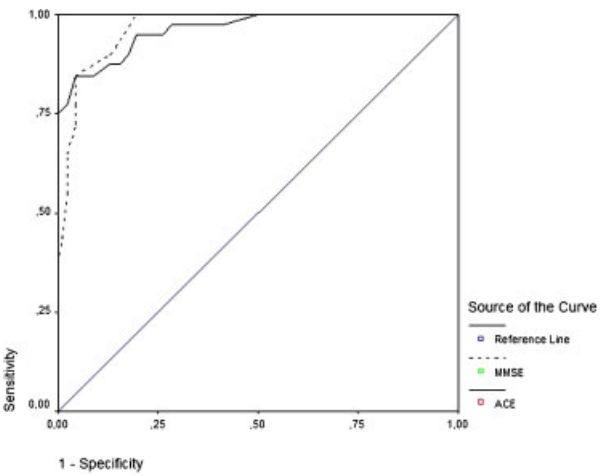

Figure 3. Comparison of ROC curves of ACE and MMSE in participants younger than 14 years old at finishing school

Table 4. Sensitivity and specificity of different cut-off scores for diagnosing dementia with corresponding probabilities of dementia (PPV) at different prevalence rates

Complete sample				
	ACE (68)	ACE (70)	MMSE (24)	MMSE (27)
Sensitivity	0.90	0.92	0.62	0.95
Specificity	0.86	0.82	0.96	0.73
PPV (5%)	0.25	0.21	0.45	0.16
PPV (10%)	0.42	0.36	0.63	0.28
PPV (20%)	0.62	0.56	0.79	0.47
PPV (30%)	0.73	0.69	0.87	0.6
Education $\geq$ 14 years old at finishing school				
	ACE (74)	ACE (83)	MMSE (24)	MMSE (27)
Sensitivity	0.96	0.96	0.63	0.90
Specificity	0.85	0.65	0.98	0.79
PPV (5%)	0.25	0.11	0.62	0.18
PPV (10%)	0.42	0.21	0.78	0.32
PPV (20%)	0.62	0.37	0.89	0.52
PPV (30%)	0.73	0.50	0.93	0.65
Education < 14 years old at finishing school				
	ACE (65)	ACE (68)	MMSE (21)	MMSE (24)
Sensitivity	0.90	0.95	0.65	0.85
Specificity	0.83	0.79	0.98	0.96
PPV (5%)	0.22	0.19	0.63	0.53
PPV (10%)	0.37	0.33	0.78	0.70
PPV (20%)	0.57	0.53	0.89	0.84
PPV (30%)	0.69	0.66	0.93	0.90

$\leq$ 68/100 which was optimal in the complete sample (Table 4). Whereas, in the high-educational subgroup a cut-off score two standard deviations below the mean of the control group ($\leq$ 74/100) obtained a sensitivity of 96% with a corresponding specificity of 85% (Sensitivity and specificity of different cut-off scores for diagnosing dementia with corresponding probabilities of dementia (PPV) at different prevalence rates have been summarized in Table 4).

DISCUSSION

The ACE was originally devised for a population of high educational level (average 11–12 years of formal education) and validated in an outpatient sample attending a memory clinic in Cambridge (UK) (Mathuranath *et al.*, 2000). The aim of the test was to improve early recognition of AD and to diferentiate AD and FTD at an early stage. In order to attain this goal the memory and language component of the MMSE was expanded and verbal fluency was incorporated. The naming task included in the ACE was also made more difficult by adding ten drawings of medium or low frequency, and cube and clock drawing were added. The result was a reliable instrument for dementia detection that expectedly showed its superiority over the MMSE. These results were replicated in comparable samples regarding education in Belgium (Bier *et al.*, 2004; Bier *et al.*, 2005) and Argentina (Sarasola *et al.*, 2004), but it was intriguing how these changes were going to affect performance in a low-educational sample. This was particularly interesting because many of the tasks included in the ACE like phonemic verbal fluency (González da Silva *et al.*, 2004), naming tasks (Reis *et al.*, 2001), and constructional abilities (Ostrosky *et al.*, 1998) were affected by level of literacy. Our sample was splitted in two sub-groups of lower (the group of patients who finished school prior to the age of 14) and higher educational attainment (the group of patients who finished school older than the age of 14), but even the latter group can be regarded as a low-educational sample in comparison with international standards (Sarasola *et al.*, 2004; Mathuranath *et al.*, 2000).

Within the complete sample the cut-off score of 68/100 showed good psychometric properties and AUC. VLOM ratio showed its usefulness in differential diagnosis between AD and FTD, even though the cut-off point did not match that originally proposed by Mathuranath *et al.* (2000), an expected fact given that the score reduction due to educational level is not proportional in all subcomponents of the ACE. These results are discordant with those obtained in a recent study (Bier *et al.*, 2004) but this is probably due to the use of different criteria for FTD diagnosis.

In the patients' subgroup $\geq$ 14years of age at finishing school, the ROC curves showed the superiority of the ACE over the MMSE (Fig. 2). In this sample the mean total education was 6–7 years (15 years old at finishing the school) (Table 3), far from the mean education in the British sample. We propose in this population to use a cut-off score of $\leq$ 74/100, which obtained an optimal sensitivity (96%) and specificity (85%) (Table 4).

Conversely, in the low-educated group the ACE obtained an AUC similar to the MMSE, an unsurprising fact given that less than 14 years of age at finishing the school means in our population, an irregular mean schooling of 3 years (from 8–9 years old until 10–11), i.e. functional illiteracy (Table 3). It is a well known fact, that the Spanish civil war and the subsequent dramatic economical difficulties suffered by the population compelled many children, especially in

rural areas, to abandon school and become part of the labour force, a fact that accounts for this low-educational profile (Mateos *et al.*, 2000; Blesa *et al.*, 2001; García de Yébenes *et al.*, 2003). In clinical practice our proposal in this population is to use the more stringent cut-off score of $\leq 68/100$, (sensitivity 95%) even though the results of the lower cut-off point ($\leq 65/100$) are very similar (sensibility 90%, specificity 83%).

As Ostrosky *et al.* (1998) have pointed out; educational effect on neuropsychological test performance is not a linear effect. Differences between 12 and 15 years of total education are virtually none, but differences between 3 and 6 years of education (especially when, as in our sample, less than 14 years of age at finishing school means irregular schooling) can be remarkable.

Complementary results regarding educational influences on performance in the ACE will be derived from the Argentinean study (Sarasola *et al.*, 2004) carried out in a highly educated sample (mean education 12 years). This study carried out in an urban upper-class population suggests an optimal cut-off point of 86/100 (Sarasola *et al.*, 2004).

In addition to the quantitative analysis we would like to comment on a clinical impression that is currently being tested. Due to the socioeconomic circumstances previously quoted, an important migratory stream departed from Galicia during the 1950s to the 1970s, firstly to South-America and then to Central Europe. This population has returned during the last decade or is returning now in part to benefit from welfare policies. Even though these patients had the same formal educational level as their contemporaries who did not emigrate, their performance on neuropsychological testing is much better. Our hypothesis is that working and living in cognitively more demanding environments has functioned as an 'informal schooling', a variable that is important to take into account. Return migration must be assessed when exploring cognitive performance, especially when the majority of control samples are composed of non-migrants.

We can conclude that the Spanish version of the ACE is a useful instrument for diagnosing dementia even in populations with low-educational profile. Further studies are warranted in order to study the effect on the ACE of culture, education and age in different cultures and settings.

KEY POINTS

- The Addenbrooke's Cognitive Examination (ACE) is a midi-battery that incorporates the MMSE, expanding memory, language, visuospatial components and adding tests of verbal fluency.
- Our sample was splitted in two sub groups of lower and higher educational attainment, but even the latter group can be regarded as a low-educational sample in comparison with international standards.
- ROC curves demonstrated the superiority of the ACE in the sub sample of patients that finished school at over 14 years old (mean 6–7 years of total education).
- The use of the ACE (Spanish version) is free to all bone fide clinical users. Copies for private clinical use can be obtained from the authors.

ACKNOWLEDGEMENTS

The authors are grateful to Prof. FJ. Jorge, Dr. T. Bak, Dr. G. Ozaita and Dr. T. González for their help. The authors wish to thank the anonimous referees for their comments. This work was supported by a Xunta de Galicia research grant PGIDIT 03SAN 92302. Part of this work merited the XIX Cabaleiro-Goas award of the Galenus Auriensis Fundation.

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