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ORIGINAL ARTICLE

Validation of the Spanish Version of the Addenbrooke's Cognitive Examination-Revised (ACE-R)

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Abstract
Background: The Addenbrooke's Cognitive Examination Revised (ACE-R) is an improved version of the earlier brief screening test which has been validated in English with high sensitivity and specificity to detect cognitive dysfunction. The aim of this study was to validate the Spanish version of the ACE-R in an Argentine population.
Methods: A group of patients with Alzheimer Disease (AD) and patients with behavioural variant Frontotemporal Dementia (bvFTD) paired by age, sex, and years of education with healthy controls were assessed using the ACE-R. Stage of dementia was measured with the Clinical Dementia Rating Scale (CDR). The English version of the ACE-R was first translated into Spanish and then back-translated into English by two blind independent experts.
Results: Internal reliability was very good (Cronbach's alpha=0.89). Concurrent validity, determined by the correlation between total ACE-R and CDR was significant ($P<.001$) and inter-rater reliability was excellent (Cohen's kappa=0.98). Controls significantly outperformed AD and bvFTD patients on most subdomains of the ACE-R, with significant differences between the dementia groups. With a cut-off score of 85 points, sensitivity was 97.5% and specificity was 88.5%, with a likelihood ratio of 99.3 for the detection of dementia. The ACE-R showed higher sensitivity than the MMSE for the *detection of dementia*.
Conclusions: The Spanish version of the ACE-R is a brief yet reliable screening tool for the detection of early cognitive impairment and has shown to discriminate between bvFTD and AD.

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PALABRAS CLAVE
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Validación de la versión en español del Addenbrooke's Cognitive Examination-Revisado (ACE-R)

Resumen
Introducción: El Addenbrooke's Cognitive Examination-Revisado (ACE-R) es una actualización del test de cribado ACE, cuya versión en inglés ha demostrado una alta sensibilidad y especificidad para detectar disfunción cognitiva en pacientes con demencia. La versión original del ACE ya ha sido adaptada y validada en castellano. El objetivo del presente estudio fue adaptar y validar en una población argentina la versión revisada del mismo.
Métodos: Un grupo de pacientes con enfermedad de Alzheimer (EA) y pacientes con la variante conductual de la demencia frontotemporal (vcDFT) apareados por edad, sexo y años de educación y un grupo control fueron evaluados con la versión en español del ACE-R. La severidad de la demencia fue medida con el Clinical Dementia Rating Scale (CDR), incluyéndose únicamente pacientes en los estadios tempranos de ambas afecciones. La versión en inglés del ACE-R fue traducida al español y luego retraducida al inglés por dos expertos independientes ciegos a la versión original.
Resultados: La fiabilidad interna fue alta (alfa de Cronbach = 0,89). La validez concurrente, determinada por la correlación entre el ACE-R y el CDR, fue estadísticamente significativa ($p < 0,001$) y la concordancia entre evaluadores fue excelente (kappa de Cohen = 0,98). Los sujetos control obtuvieron puntajes estadísticamente superiores a los pacientes con EA y vcDFT en la mayoría de los subdominios del ACE-R, encontrándose diferencias significativas entre ambos grupos de demencia. Con un puntaje de corte de 85 puntos, la sensibilidad fue del 97,5% y la especificidad del 88,5%, con un cociente de probabilidades de 99,3:1 para la detección de demencia. El ACE-R presentó una sensibilidad más elevada que el MMSE para la detección de demencia.
Conclusiones: La versión en español del ACE-R es una herramienta breve y válida para la detección temprana del déficit cognitivo asociados a demencia y ha demostrado ser de utilidad para la diferenciación entre AD y vcDFT.

Introduction

In view of the prevalence of dementia and the social costs it entails, its early detection is particularly important, especially considering the advent of new therapeutics. The validation of cognitive screening tests that are efficient but, at the same time, quick and easy to administer and accessible for primary health-care has become a prime necessity in clinical practice.

The Mini-Mental State Examination (MMSE)[1] is the screening tool most widely used and validated in dementias. However, this tool presents major difficulties for the detection of dementia in its initial stages. First of all, changes in memory and language are the initial symptoms in Alzheimer's Disease (AD) and MMSE presents low sensitivity in the detection of these deficits. Secondly, the MMSE also presents low sensitivity for the objective detection of executive deficits, which are characteristic of other high-prevalence dementias, such as frontotemporal dementia (FTD). In order to overcome the weaknesses of the MMSE, Mathuranath et al.[2] developed Addenbrooke's Cognitive Examination (ACE) as a cognitive screening tool that was, in addition to brief (between 15 and 20 min) and easily administered, sensitive for the detection and differentiation of the most prevalent dementias. Over these years, the ACE has gained great popularity in clinical practice and has been adapted to several languages,[3-6], including Spanish by our team.[7,8] This tool is currently used a great deal in Spain and Latin America. In addition, it has been administered in different clinical populations and has been shown to be capable of detecting cognitive impairment in AD,[2] in FTD,[9] in progressive supranuclear palsy (PSP), in corticobasal degeneration, in multi-systemic atrophy and in Parkinson's disease.[10] The authors of the ACE have proposed a coefficient called VLOM as a tool within the ACE capable of distinguishing FTD from a dementia such as Alzheimer's. This coefficient is obtained by adding the scores for verbal fluency (maximum: 14) to those for language (maximum: 28) and dividing the result by the sum of the orientation scores (maximum 10) plus the deferred recall of learnt names and addresses (maximum 7).

In order to improve the original version, a new version of the test was developed in 2006: the Addenbrooke Cognitive Examination-Revised (ACE-R).[11] The ACE-R incorporated changes based on the experience of the group of ACE authors following the repeated use of their original version. The changes in the design were made to facilitate administration and the amendments to the content were aimed at permitting an easier transcultural use of the test and at increasing its levels of sensitivity and specificity.[11] The

most prominent changes were: *a)* the increased level of difficulty in the denomination of objects in order to avoid the "ceiling effect" and improve the complexity and variety of the visual-spatial stimuli as these were few and limited; *b)* the creation of alternative formats (versions A, B and C) with different stimuli for the evocation of the name and address to avoid the learning effect from repeated assessments, and *c)* finally, the 26 individual components are combined to produce 5 sub-scores, each representing a specific cognitive domain and contributing relatively in line with the total score.

To our knowledge, the ACE-R has not been validated in Spanish. The goal of the present paper has been to validate the adaptation to Spanish of the ACE-R in a highly-educated population in Buenos Aires, Argentina, in order to enable its standardized use as a cognitive screening test in both clinical practice and research for the detection of cognitive impairment in patients with two of the most prevalent dementias: AD and bvFTD. Furthermore, this study tries to analyze the usefulness of certain scores derived from the ACE-R (e.g. the cut-off score, the VLOM score) in its ability to differentiate these types of dementia.

Methods

Participants

A total of 127 participants attending our clinic consecutively (Cognitive Neurology Institute, "INECO", Buenos Aires, Argentina) were prospectively recruited into this study and classified into three groups: *a)* patients diagnosed as having the behavioural variant of frontotemporal dementia (bvFTD, n=41); *b)* patients diagnosed as having Alzheimer's Disease (AD, n=46), and *c)* healthy control subjects (n=40). The healthy controls did not present any history of neurological or psychiatric disorders; patients diagnosed as having AD met the criteria of the NINCDS-ADRDA,[12] and all the patients in the bvFTD group me the consensus criteria.[13] All patients were assessed through a structured interview, a neurological examination and a laboratory analysis as well as a detailed neuropsychological assessment. Furthermore, magnetic resonance imaging studies were performed on all patients. Patients with a score of 2 or more points on the Clinical Dementia Rating Scale (CDR)[14] were excluded from the study to ensure the inclusion solely and exclusively of patients in the early stages or mild involvement. None of the subjects included in this study presented diagnostic criteria of depression. The participants in the control group did not present any cognitive complaints or any history of neurological or psychiatric disorders and were not taking any medication that might affect their cognitive performance. The present study was approved by the Ethics Committee at the Cognitive Neurology Institute (INECO), in accordance with the regulations established in the Declaration of Helsinki for research with human participants.

Adaptation of the ACE-R in Spanish

The adaptation of the ACE-R to Spanish stipulated two procedures: one aimed at the production of an exact translation of the elements independent of the cultural context (e.g. instructions for the examiner) and a complementary procedure aimed at the adaptation of the stimuli associated with cultural valences (e.g. name and address of the memory item, language items, etc.). The first was achieved through two translations from English to Spanish based on the original ACE-R, followed by back translations from Spanish to English. The adaptation of specific stimuli was done on a collaborative basis drawing on our prior experience in the adaptation of the original version of the ACE[2] and by consultation with other research groups performing similar tasks in other languages. The Spanish version of the ACE-R can be requested from the authors or accessed at www.ineco.org.ar.

Procedure

All patients signed the informed consent prior to their inclusion in the research. The diagnosis of AD and bvFTD was reached on the basis of the criteria presented above and the patients were assessed using the Spanish version of the ACE-R presented here. The degree of dementia was determined through the information provided by the carers or relatives in the CDR, for which the "sum of boxes" score (CDR-sob) was calculated as the sum of the scores in each of the six items on the scale. The CDR-sob was used in the correlation analyses with the ACE-R in order to have a scale with greater amplitude and variability than that provided by the transformed CDR (0, 0.5 and 1 point).

Statistical analysis

The statistical analyses were performed using the "Statistical Package for the Social Sciences 17" (SPSS Inc., Chicago, IL). The demographic data were compared between the groups using single-factor ANOVA with *post hoc* Bonferroni comparisons where necessary. For categorical variables (e.g. gender), 2 x 3 contingency tables were used, applying the Freeman-Halton extension of Fisher's test. The internal validity was determined with Cronbach's alpha and the concurrent validity with Spearman's correlation between the total ACE-R and CDR-sob scores. The sensitivity and specificity values were determined using the ROC analytical curve between the healthy control subjects and patients with dementia, and the analysis of the cut-off score was derived from the discriminant results of the ROC curve. In addition, the odds ratio was calculated to determine the probability that a given score on the ACE-R could be derived from a patient with dementia. In the same way, inter-examiner concordance was determined using Cohen's kappa coefficient through a single simultaneous application with two examiners, blind with regard to the other's score, on a total of 30 protocols (10 from each group chosen at random).

Results

Psychometric properties

The internal validity of the Spanish version of the ACE-R was very good (Cronbach's alpha=0.89). The concurrent validity

Table 1 Demographic, clinical and neuropsychological data of the study participants

	Control (11 M, 29 F) Media (DE)	AD (12 M, 34 F) Mean (SD)	bvFTD (9 M, 32 F) Mean (SD)	Control vs AD	Control vs bvFTD	AD vs bvFTD
Age (years)	71.5 (5.6)	73.4 (5.7)	70.0 (9.3)	NS	NS	NS
Education (years)	13.0 (3.8)	12.9 (4.6)	12.8 (5.1)	NS	NS	NS
CDR-sob	—	5.3 (1.1)	4.9 (1.5)	—	—	NS
MMSE	29.4 (1.1)	22.0 (5.5)	25.0 (3.0)	**	**	NS
ACE-R total	94.3 (4.2)	64.2 (16)	78.1 (9.4)	**	**	**
Attention/ orientation	17.9 (0.4)	13.4 (4.2)	15.6 (3.4)	**	**	**
Memory	23.9 (2.3)	11.6 (5.3)	18.2 (2.7)	**	**	**
Fluency	11.9 (1.5)	6.9 (2.4)	8.1 (2.7)	**	**	**
Language	25.2 (1.1)	20.3 (2.2)	23.7 (2.2)	**	NS	**
Visual-spatial	15.4 (1.1)	12.0 (3.3)	12.9 (3.7)	**	**	NS
VLOM Coefficient	2.39 (0.3)	4.61 (2.7)	3.08 (2.1)	*	**	**

ACE-R: Addenbrooke's Cognitive Examination Revised; CDR-sob: Clinical Dementia Rating Scale-sum of boxes; AD: Alzheimer's Disease; M: males; F: females; MMSE: Mini Mental State Examination; NS: not significant; bvFTD: behavioural variant of frontotemporal dementia.

*p<0.05. **p<0.001.

with CDR-sob was shown to be high (r=−0.58, p<0.01), with a negative correlation coefficient showing that the values of the total ACE-R as a whole became smaller the severity of the dementia, as measured with CDR, increased. The concurrent validity with a simpler screening tool such as MMSE was shown to be high (k=0.93, p<0.0001). The coefficient for the inter-rater concordance was excellent (Cohen's kappa=0.98).

Demographic and neuropsychological variables

As shown in table 1, no significant differences were observed with respect to age ($F_{2,124}$=2.02, k=0.23), years of formal education ($F_{2,124}$=1.82, p=0.26) or gender (x^2=0.26, df=2, p=0.88) between the groups. No significant differences were observed between patients with AD and bvFTD with respect to the severity of their dementia, in accordance with the CDR-sob values (t_{85}=0.69, p=0.56). On the MMSE ($F_{2,124}$=40.8, p<0.001), significant differences were observed between the control groups and the AD group (p<0.001) and bvFTD (p<0.001), but not between the two dementia groups (p=0.99). On the other hand, with respect to the total score on the ACE-R ($F_{2,124}$=75.9, p<0.001), as well as both groups of patients differing significantly from the controls (p<0.001, for both groups), the dementia groups were significantly different from each other (p<0.001). The same pattern was found in the sub-scales for orientation/ attention ($F_{2,124}$=27.7, p<0.001), memory ($F_{2,124}$=78.6, p<0.001) and fluency ($F_{2,131}$=52.2, p<0.001). Nonetheless, on the visual-spatial sub-scale ($F_{2,124}$=17.2, p<0.001), a significant difference was observed between the controls and the AD group (p<0.001 in both cases) and bvFTD (p<0.001 in both cases), but not between the dementia groups (p=0.96). On the language sub-scale ($F_{2,124}$=23.2, p<0.001), the patients with AD had a significantly worse performance than the controls (p<0.001) and the patients with bvFTD (p<0.001), these two latter groups did not differ from each other (p=0.17).

Diagnostic properties

Sensitivity and specificity were determined through a discriminant analysis using the ROC curve (fig. 1). Although the cut-off scores suggested by the English version of the ACE-R[11] were 82 and 88, on the basis of our data with the version in Spanish, a cut-off score of 85 points was identified as the value potentially most accurate for the diagnosis of dementia with this tool, associated with the best balance between sensitivity and specificity. In line with this, with a cut-off score of 85/100, we detected a sensitivity of 97.5% and a specificity of 88.5% in the detection of dementia (AD and bvFTD) versus the control subjects. After analysis as a whole, the odds ration for dementia presented a high value: 99.3.

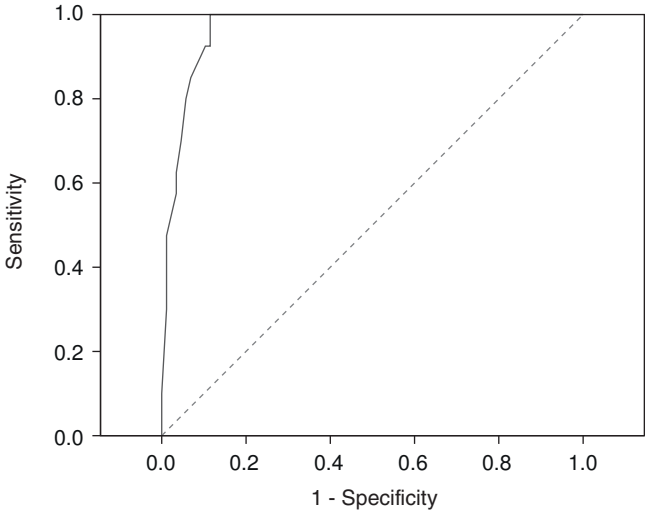

Figure 1 ROC curve showing the sensitivity and specificity associated with the cut-off score identified in our data (85/100) for the detection of dementia.

The VLOM coefficient, calculated as the proportion between the verbal fluency plus language scores (VF+L) and the scores for orientation and long-term memory evocation of the address in the memory test (O+M), has been put forward as a way to distinguish AD from FTD.[2,11] In our sample, significant differences were observed between patients with both pathologies using this value (t_{85}=2.21, p=0.03), suggesting their potential usefulness in the distinction of both types of dementia. A VLOM value of 3.5 or more distinguished patients with AD from bvFTD with a sensitivity of 81% and a specificity of 79%.

Discussion

The present study shows that the Spanish version of the ACE-R is a useful tool for the detection of cognitive dysfunction in dementia and validates it for standardized use in clinical applications and research in Spanish-speaking populations with a high level of education.

The ACE-R was shown to be an improved version with respect to the publication of the original ACE, presenting better sensitivity and specificity values as a consequence of the changes made to the previous version (especially in connection with the domains of language and visual-spatial abilities). Furthermore, it was shown to be capable of detecting cognitive dysfunction in both FTD and AD, even in its initial stages. While the English version of the ACE-R proposes two cut-off points (82 and 88 points), our study shows that the cut-off point identified as the most appropriate balance between sensitivity and specificity was 85 points (out of 100). The Spanish version of the ACE-R also presented a very good internal consistency and concurrent validity with other cognitive-functional screening tools, such as CDR.

On the other hand, the version of the ACE-R in Spanish was seen to be, in addition to a sensitive tool for the detection of cognitive dysfunction in patients with bvFTD and AD, capable of discriminating between the two conditions. Patients with AD and bvFTD presented significantly different scores on the ACE-R on the sub-scales for attention/orientation, memory, language and fluency. These differences were all in favour of patients with bvFTD. These results can be interpreted bearing in mind that the main cognitive alteration in the behavioural variant of frontotemporal dementia is an insidious deficit specifically prominent in executive functions, due to early changes in the structure of the frontal lobe (for a review, please refer to Hodges & Miller[14]). Therefore, it might be expected that patients with bvFTD will present better scores than patients with AD on the different ACE-R sub-scales. Notably, the only sub-scale on which no significant differences were found between the two dementia groups was on the visual-spatial sub-scale; both were significantly different from the control group. This lack of significant differences between the two conditions on the visual-spatial scale might be explained as follows: both the patients with AD and those with bvFTD showed lower scores in comparison with the control group, but the deficits observed in patients with AD might be due to the visual-spatial failures characteristic of this disorder, mainly based on parietal involvement, whereas the deficits in patients with bvFTD might be influenced most by the executive components inherent to visual-spatial tasks. This might be reflected in the tasks of copying the cube and building the clock. Future studies must assess whether there are subtle elements of a more qualitative nature with regard to the visual-spatial tasks allowing a distinction to be made between the performance of patients with AD and bvFTD based on the ACE-R.

From what has been said above, an appropriate screening test that attempts to differentiate between the two pathologies of AD and bvFTD should conduct a detailed assessment of the executive functions, in addition to the remaining cognitive functions. An example of this kind of tool is the FAB[15] or INECO Frontal Screening (IFS),[16] which manage, in a short space of time, to capture executive dysfunction with high sensitivity and specificity.

In conclusion, the Spanish version of the ACE-R has been shown to be a sensitive tool for the detection of cognitive dysfunction in patients with dementia, and is capable of differentiating between AD and bvFTD. Nonetheless, considering that the ACE-R devotes little relative weighting to the executive functions, and with the ultimate goal of increasing its sensitivity even more for the detection of executive deficits especially in conditions with frontal involvement such as bvFTD, we suggest its combination with an executive screening tool.

In order to be able to contribute to this differentiation, the VLOM coefficient has been put forward in the English version of the test as a tool to discern between AD and FTD.[2,11] In our study, the potential of this coefficient revealed in previous studies was replicated, demonstrating its usefulness in our population for differentiating between these two types of dementia. This ability of the VLOM coefficient in the differentiation of AD and bvFTD is consistent with the findings of other groups in previous versions of the ACE in our language.[7,8]

The present study has some limitations. Firstly, our group of patients has a high level of education (an average of 12.9 years' schooling), which means it is not representative of the whole population of Argentina, so it is likely that future studies will be needed to investigate the usefulness of ACE-R in Spanish-speaking patients with AD and bvFTD of a lower educational level. Secondly, no test/retest was performed on the sample of patients presented here. This could be explained by the context in which the study was conducted as part of their clinical treatment, so the need for an extra appointment would enormously limit the number of patients involved in the present study. Thirdly, as has been mentioned already, it is possible to distinguish today three large groups of clinical syndromes in frontotemporal dementia: *a)* the behaviour variant (bvFTD); *b)* primary progressive aphasia involving several fluency (semantic dementia) and non-fluency dementias, and *c)* the motor variants associated with motor neuron disease. In the present study, only patients with the behavioural variant of FTD were included. The fact that patients with temporal variants of FTD were excluded reduces the generalization of the results. Further studies are needed to include the other two temporal variants of the FTD, non-fluency primary progressive aphasia and semantic dementia, in order to identify the usefulness of a tool such as ACE-R to characterize cognitive profiles.

With the growing need to identify the cognitive profile of our patients at an early stage so as to detect the onset of dementia in a clinical context, and considering that it is not always possible to assess patients with complete neuropsychological batteries, whether due to a lack of material or human resources, or else due to time constraints, it is of vital importance to develop and validate screening tools such as the ACE-R. These tools provide health-care professionals with a valuable source of information in a short space of time.

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Conflict of interest

The authors have no conflict of interest to declare.

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