

Original Research Article

Validity of Addenbrooke's Cognitive Examination to Discriminate between Incipient Dementia and Depression in Elderly Patients of a Private Clinic in Lima, Peru

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Key Words

Dementia · Depression · Differential diagnosis · Addenbrooke's Cognitive Examination

Abstract

Background/Aims: Dementia and depression are different clinical conditions, but share common features, and can be indistinguishable in the initial disease stages. We aimed to establish whether the Peruvian version of the Addenbrooke's Cognitive Examination (ACE-Peru) can distinguish between the cognitive profile in patients with incipient dementia and that in patients with depression. **Methods:** This was a cross-sectional study to assess the performance on the ACE-Peru of 193 elderly subjects (102 with dementia, 21 with depression, and 70 healthy controls). Depending on the diagnosis, there were two groups of cognitive impairment (CI) – the primary neurodegenerative (PN-CI) subtype and the secondary to depression (SD-CI) subtype – as well as a non-CI group. The area under the curve (AUC) of the receiver-operating characteristic curve was determined to compare the diagnostic performance, using the diagnosis of CI as the gold standard. **Results:** In our sample of elderly subjects aged 59–82 years with at least 7 years of education, the ACE-Peru showed a significantly better performance than the MMSE (AUC = 0.997 vs. AUC = 0.887; $p < 0.05$) for the discrimination between PN-CI and SD-CI. **Conclusions:** The ACE-Peru is able to distinguish between the cognitive profile in patients with incipient dementia and that in patients with depression.

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Introduction

Dementia is considered to be one of the main geriatric problems due to impaired functionality and independence [1]. The estimated prevalence of senile dementia in Latin America is 8.5% among people older than 60 years [2–8]. There is also an increase in new therapeutic options [9]. For this reason diagnostic tools which make early case detection possible need to be available. Thus, serial instruments have been developed, such as the Mini-Mental State Examination (MMSE) [10], the Mental Cambridge Disorders of the Elderly Examination (CAMDEX) [11–13], and its cognitive component, the Cambridge Cognitive Examination (CAMCOG) [14], as well as the Dementia Rating Scale (DRS) [15–18].

Although the MMSE is the instrument most frequently used, it lacks sufficient sensitivity to detect mild impairment observed in the early stages of Alzheimer's dementia (AD) as well as other changes in frontotemporal dementia (FTD) [19]. Moreover, CAMCOG, DRS, and the neuropsychological assessment [ideal instruments to assess cognitive impairment (CI)] are complex and need highly trained personnel and specialized equipment [20], which is usually not available at the primary care level. The Addenbrooke's Cognitive Examination (ACE), which is simpler and does not need complex equipment, could be performed at the primary care level. In other studies, it has shown a promising diagnostic performance. Thus, it is a valuable alternative in cases of early detection of dementia by general practitioners.

Depression is another common problem [21] in the elderly population [21], affecting between 13 and 18% of people older than 65 years [22, 23] and up to 40% of patients with comorbidities [24, 25]. More than half of the cases of depression late in life are secondary to the consumption of some legal drugs (depression secondary to drugs) or to the coexistence of another underlying medical condition (depression secondary to medical conditions) such as CI [22]. Dementia and depression often have various common features: (1) patients with dementia can present depressive symptomatology, (2) patients with depression can present significant CI (i.e. 'pseudodementia'), and (3) depression can be an early reaction to any CI, an early symptom of dementia, or a risk factor for dementia [26]. In some cases it is therefore difficult to establish whether the CI is secondary to an incipient organic process, as observed in AD, or to an affective disorder such as depression [27]. The staging becomes even more complicated in case of the co-occurrence of both conditions, which cannot be distinguished from one another [26, 28]. Thus, the differential diagnosis of dementia and depression represents one of the most frequent clinical problems [28].

This problem is particularly relevant in the practice of primary health care, since it has been observed that nonspecialist medical doctors do not recognize up to 21% of the cases of dementia, while 20% of nondemented subjects are misdiagnosed as having dementia [29]; in fact, only 50% of the patients with dementia are detected by medical professionals [30]. This reveals that general practitioners need diagnostic tools which allow dementia screening at the early stages of disease and which are easily applicable in the daily practice in primary care centers.

Previously, the performance of the ACE to discriminate between dementia and depression has been evaluated, although the results have been contradictory [31–34]. The following factors still need to be established: the utility of the Peruvian version of the ACE (ACE-Peru) for these purposes, the appropriate cutoff value, and the need for its adjustment for variables such as gender, age, and years of education.

This study assesses the validity of the ACE-Peru in discriminating between the CI associated with depression and the CI secondary to incipient dementia in patients older than 55 years, as well as in discriminating between the CI secondary to depression and the absence of CI. Additionally, the performance of the ACE-Peru was compared with the MMSE based on each test performance evaluated against the gold standard.

Materials and Methods

Design of the Study

This is a secondary analysis of the database derived from the implementation of a guideline-based diagnostic protocol for dementia in the Service of Neurology of a private clinic in Lima, Peru. Previously, this database has been partially used for the validation of the ACE-Peru [35].

Population and Sample

For this analysis we included the data of patients older than 55 years, who had Spanish as their native language, who had at least 6 years of education, and who visited the Neurology Consulting Room during the period between April 2006 and April 2009. The cases were selected among those patients who reported cognitive problems (subjective cognitive impairment, SCI) that were confirmed for an applied screening test (objective cognitive impairment, OCI). Healthy subjects were selected among the relatives of non-SCI and non-OCI patients.

We excluded those subjects with structural and/or functional deficits (visual or auditory deficits) that affect their performance and interfere with the carrying out of the cognitive tests, subjects with a history of diseases associated with secondary CI [e.g. cerebrovascular illness, hypothyroidism, and central nervous system infections (HIV or syphilis), severe encephalic traumatism, and subdural hematoma], subjects with a history of conditions associated with secondary CI (e.g. vitamin B12 deficiency, chronic hepatopathy, or nephropathy, and addiction or abuse of substances), as well as subjects with a score of more than 4 on the Hachinski index (which suggests underlying cerebrovascular deficits).

Procedures

According to the diagnostic protocol (the gold standard for this study), first CI screening was carried out to establish the cognitive status. Second, the etiologic diagnosis of CI was assessed and also the diagnosis of depression, whenever dementia was found to be absent. Finally, the classification of dementia was established in demented patients. Both the tests of interest and the gold standard were systematically and independently assessed in all consecutive eligible patients.

Stage 1: Screening

CI screening was carried out by means of the application of the questionnaire for the assessment of subjective memory complaints [36], the MMSE [10] and the Clock-Drawing Test, Manos' version [37]. The Pfeffer Functional Activities Questionnaire (PFAQ) was used for functional evaluation [38]. Those patients with at least one positive test in CI screening were classified as OCI.

Stage 2: Etiologic Diagnosis

Clinical assessment including Beck's Depression Inventory (BDI), laboratory tests, and brain CT scans/magnetic resonance neurography were applied to investigate the main causes of CI, so as to ascertain whether patients had dementia, depression, or another condition. For those patients who presented some cause of SCI, appropriate treatment was offered. When we observed a posttherapeutic CI, the patients were classified as secondary CI, like those patients with medical conditions where CI is naturally irreversible. Those patients, in whom no specific cause of CI was identified, were classified as primary CI.

Stage 3: Dementia Subtype Diagnosis

All patients with primary CI were submitted sequentially to the neurological and neuropsychological evaluation for the dementia diagnosis, which was carried out by a team of professionals including two neurologists and one neuropsychologist.

The neurologists performed an integral neurological evaluation and applied the neuropsychiatric battery: Neuropsychiatric Inventory (NPI). The neuropsychologist applied a battery which consisted of the following 9 tests: Rey Auditory Verbal Learning Test, Logical Memory Subtest of Wechsler Memory Scale-Revised, Trail Making Test A and B, Rey's Complex Figure, Test of Denomination of Boston, Wisconsin Card Sorting Test, Letter-Number (Wechsler Adult Intelligent Scale III Subtest), and Digit Span.

The definitive dementia diagnosis (dementia subtype) was based on a consensus between the professional team members according to appropriate diagnostic criteria. The applied criteria were the following: (1) Diagnostic and Mental Statistical Manual of Disorders, 4th Edition, Text Revision (DSM-IV-TR) for the dementia diagnosis, (2) National Institute of Neurologic, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for the AD diagnosis, (3) consensus of Neary for the FTD diagnosis, (4) United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) for the diagnosis of Parkinson's disease (PD), and (5) American Academy of Neurology (AAN) for the diagnosis of mild CI (MCI). Although MCI is not a dementia subtype, it has been recognized as a dementia precursor [39].

We used the term primary neurodegenerative CI (PN-CI) for the demented patients without considering those with predementia (MCI). The cases of CI secondary to depression (SD-CI) were defined as patients with secondary CI; those with medical causes of CI (other than depression) or with a BDI value suggesting depression (BDI ≥ 13 points) were excluded. The group of cognitively healthy subjects was selected from the healthy relatives of the patients, in whom we applied the same diagnostic protocol for CI to exclude subjects with CI.

All evaluations were done blinded and independently by one neurologist who applied the ACE to all the participants at the end of stage 1 (screening), before Beck's test application, and long before the definitive establishment of the diagnosis. For this study we included patients with incipient organic dementia (AD, FTD, and PD dementia), patients with depression, and subjects without CI (healthy control group).

Statistical Analysis

Sociodemographic variables were compared with χ^2 and Mann-Whitney tests for pairs of groups (PN-CI vs. SD-CI and SD-CI vs. healthy group). Sensitivity and specificity of the ACE and the MMSE were calculated.

As both the ACE and the MMSE are continuous variables, we sought to assess their diagnostic performance for different threshold values. For this we estimated the area under the curve (AUC) for the receiver-operating characteristic (ROC) curves for the ACE and the MMSE. The analysis was performed by using STATA 12.0 (Stata Corp., College Station, Tex., USA).

Ethical Aspects

This study was authorized by the Investigation and Teaching Unit of the Clínica Internacional. The present study was approved by the Ethics Committee of the Universidad Peruana Cayetano Heredia.

Table 1. Demographic characteristics and test scores in 193 subjects attending the Neurology Consulting Room of the Clínica Internacional

	SD-CI (depression group; n = 21)	PN-CI (dementia group; n = 102)	Non-CI (healthy group; n = 70)	p value (SD-CI vs. PN-CI)	p value (SD-CI vs. non-CI)
Males	10 (47%)	49 (48%)	36 (51%)	0.972 ^a	0.759 ^a
Age, years	66 (59–72)	69 (61–82)	68 (62–80)	0.002 ^b	0.018 ^b
Education, years	10 (8–16)	10 (7–18)	11 (7–18)	0.470 ^b	0.364 ^b
MMSE score	27 (25–29)	23 (16–29)	29 (27–30)	<0.001 ^b	<0.001 ^b
ACE score	88 (83–92)	71 (56–84)	94 (89–98)	<0.001 ^b	<0.001 ^b

Data are presented as median (range) unless indicated otherwise. ^a p value for the χ^2 test. ^b p value for the Mann-Whitney test.

Results

A total of 193 subjects were included, of whom 102 were patients with PN-CI (53 with AD, 26 with FTD, and 23 with dementia for PD), 21 were patients with SD-CI, and 70 were cognitively healthy subjects.

Significant differences were observed by age, ACE, and MMSE values between the subjects with PN-CI and healthy subjects compared to those with SD-CI (table 1). This is critical because the age is recognized as an influential factor on the cognitive performance, which is evaluated by these tests. Thus, lower values are expected in the ACE or the MMSE as the age increases.

Accordingly, we observed that the age is significantly lower between the patients with SD-CI compared to other groups. This could influence the ACE and the MMSE values, which are observed to be significantly higher in patients with PN-CI (who were oldest). Nevertheless, this significance cannot only be explained by age, since the patients with SD-CI had lower values than the healthy subjects, although the former were older. No significant differences were observed by sex and years of education.

The ACE showed a high precision in discriminating between PN-CI and SD-CI (AUC = 0.997; 95% confidence interval 0.99–1.00) and in discriminating between SD-CI and non-CI (AUC = 0.948; 95% confidence interval 0.90–0.99). Although the ACE had a significantly better performance than the MMSE in discriminating between PN-CI and SD-CI (fig. 1), there were no similar performances in discriminating between SD-CI and non-CI (fig. 2).

Regarding the clinical implications, in every patient with CI in a similar context, the application of the ACE will allow to establish whether CI is caused by dementia or depression with an almost perfect precision, at high sensitivity and specificity rates (90 and 100%, respectively), using a cutoff value of at least 85 points. The use of this cutoff value results in 98.37% of correctly classified subjects (table 2).

Discussion

This study aimed to assess the utility of the ACE-Peru in order to discriminate between dementia and depression in patients with CI, showing a high discriminative performance. We found a high sensitivity (90%) and a perfect specificity (100%) when the ACE was applied using a cutoff value of 85. These findings are consistent with those reported previously by other studies [32–34].

Table 2. Cutoff values and diagnostic utility of ACE and MMSE to discriminate between SD-CI and PN-CI in 193 subjects attending the Neurology Consulting Room of the Clínica Internacional

	ACE	MMSE
<i>Discrimination between patients with SD-CI and patients with PN-CI</i>		
Optimal cutoff value ^a	85/86	27/28
Sensitivity	0.90	0.67
Specificity	1.00	0.88
Area under the curve	0.997 ^b	0.887
<i>Discrimination between non-CI subjects and patients with SD-CI</i>		
Optimal cutoff value ^a	90/91	28/29
Sensitivity	0.97	0.97
Specificity	0.67	0.67
Area under the curve	0.948	0.895

^a The cutoff value is based both on sensitivity and specificity to obtain a maximum percentage of correct classification.

^b Significant difference with regard to the MMSE, $p < 0.05$. Gold standard: final diagnosis achieved with the application of the diagnostic protocol for CI.

Fig. 1. ROC curves for the discrimination between SD-CI and PN-CI by means of the ACE in comparison to the MMSE in 193 subjects attending the Neurology Consulting Room of the Clínica Internacional.

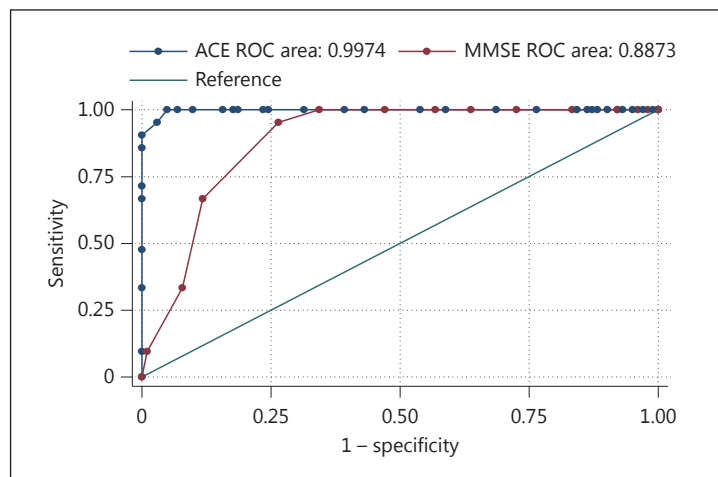
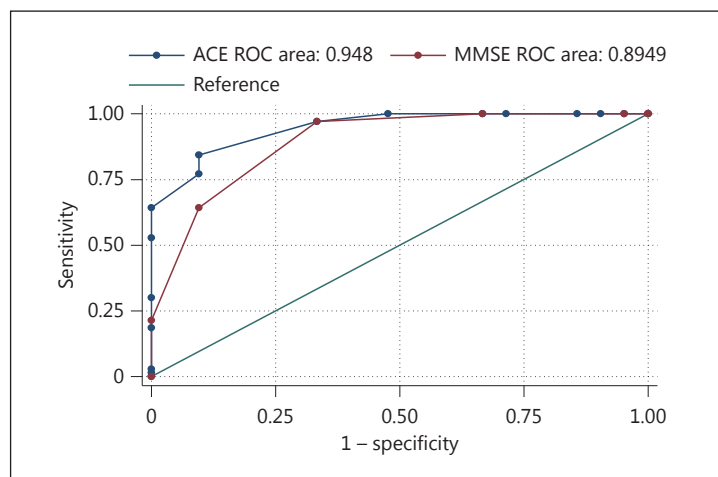


Fig. 2. ROC curves for the discrimination between SD-CI and non-CI by means of the ACE in comparison to the MMSE in 193 subjects attending the Neurology Consulting Room of the Clínica Internacional.



Dementia is defined as the presence of CI of two or more cognitive domains [memory and other cognitive domain(s)] [40]. Depression is defined as the absence of positive affectivity and low mood [41]. Although dementia and depression are different clinical entities, they share common features: (1) impairment of attention and working memory, (2) changes in sleep patterns, and (3) reduction of social and work-related functionality [42]. These problems have led to mistakes in medical practice. Thus, a study has found that at least 26 of every 100 patients were misdiagnosed as having dementia, 15 of whom were patients with nonrecognized depression [27]. Similarly, it is possible that some patients with depression could be misdiagnosed as having dementia, resulting in a subdiagnosis of depression. This situation has not been previously studied.

Although the cutoff value of 85 sacrifices sensitivity to maximize specificity, we believe it is appropriate because of the need to prioritize the ability of the ACE to rule out a depressive disease (suggesting a dementia disease) in every elderly patient with CI. The importance of this tool in primary health care is potentially valuable for the early detection of demented patients and their timely referral to specialized centers. Finally, the identification of patients with CI truly secondary to depressive disease is highly important for the prognosis, because appropriate treatment of depression in SD-CI patients can improve the quality of life and can even achieve a full resolution of the CI [31].

The ACE-Peru is able to distinguish between the cognitive profile in patients with incipient dementia and that in those with depression, but not between the cognitive profile in patients with depression and cognitively healthy subjects. We recommended the use of 85 as a cutoff value for differentiating between these two medical conditions in elderly patients with CI.

It was not possible to use the best possible instruments for the measurement processes, limiting the evaluation only to data previously obtained for other purposes. Thus, the diagnosis of depression was not reached by means of the criteria listed by the International Classification of Diseases Version 10 (ICD-10) or by the DSM-IV-TR. However, we used a depression indicator (BDI), which was validated in the elderly population [43] and which is particularly useful in subjects with CI [44] such as in our study population.

Finally, previous studies [31–34] did not assess the utility of the ACE in patients with PD for our study objectives. We propose a new use for this screening test: a comprehensive and simple tool in order to discriminate between dementia and depression in elderly patients with CI, with an easy and quick application, which might be used in primary health care. We recommend assessing this application at the community level in prospective population-based studies.

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Disclosure Statement

The authors report no conflicts of interest.

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