Validation of Addenbrooke’s cognitive examination for detecting early dementia in a Japanese population

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A B S T R A C T

There is a clear need for brief, but sensitive and specific, cognitive screening instruments for dementia. We assessed the diagnostic accuracy of the Japanese version of Addenbrooke’s Cognitive Examination (ACE) in identifying early dementia in comparison with the conventional Mini-Mental State Examination (MMSE). Standard tests for evaluating dementia screening tests were applied. A total of 201 subjects (Alzheimer’s disease (AD) = 65, frontotemporal dementia (FTD) = 24, vascular dementia = 26, dementia with Lewy bodies = 11, mild cognitive impairment (MCI) = 13, and controls = 62) participated in this study. The reliability of the ACE was very good (alpha coefficient = 0.82). In our patient series, the sensitivity for diagnosing dementia with an ACE score of ≤ 74 was 0.889 with a specificity of 0.987, and the sensitivity of an ACE score of ≤ 80 was 0.984 with a specificity of 0.867. The Japanese version of the ACE is a very accurate instrument for the detection of early dementia, and should be widely used in clinical practice.

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1. Introduction

Early detection of dementia is an important challenge for the physician, especially since the introduction of disease-modifying treatments. Screening for early dementia requires a sensitive instrument for assessment of cognition. The Mini-Mental State Examination (MMSE) is a widely used cognition screening test in many parts of the world (Folstein et al., 1975). However, it has limitations in screening multiple cognitive domains and detecting early dementia (Teng et al., 1987; Naugle and Kawczak, 1989; Feher et al., 1992). Addenbrooke’s cognitive examination (ACE) has been proposed as a simple and effective instrument to detect dementia (Mathuranath et al., 2000). Besides, it has been validated in the following languages: Malayalam (Mathuranath et al., 2004), French (Bier et al., 2005), Spanish (Garcia-Caballer et al., 2006), German (Alexopoulos et al., 2006), and Danish (Stokholm et al., 2009). Moreover, a revised version of ACE (ACE-R) has recently been made available (Mioshi et al., 2006). Here, we report our experience with this test and show that the Japanese ACE is effective in detecting dementia in a Japanese-speaking population.

2. Methods

2.1. The instrument

The ACE was translated into Japanese with some adaptations concerning the name and address learning and delayed recall tests, verbal fluency test, word and sentence repetition tests, and reading tests (Table 1). In the tests of repetition, word reading and name and address recall, replacement with words of equivalent frequency and syllable length in Japanese were made. On verbal fluency test, words beginning with the letter ‘p’ were replaced by words beginning with the syllable ‘sa’ because the Japanese language is based on syllables rather than letters. Thereafter, a bilingual expert not familiar with the original ACE translated it back into English. The retranslated version was very similar to the original one.

2.2. Subjects

We administered the ACE to 126 consecutive patients who had been referred to the Memory Clinic of Okayama University Hospital and who had been diagnosed with Alzheimer’s disease (AD), vascular dementia (VaD), frontotemporal dementia (FTD), or dementia with Lewy bodies (DLB) (Table 2). Sixty-two subjects who had no evidence of organic dementing disorders or psychiatric diseases (30 men, 32 women; age range, 40–80 years; mean age, 66.7 ± 10.1 years) and 13 subjects with a Clinical Dementia Rating (CDR) score of 0.5 without overt dementia who were recognized as having mild cognitive impairment (MCI) (six men, seven women; age range, 43–83 years; mean age, 62.7 ± 12.3 years) (Table 2) were used as a control group.

Sixty-five outpatients were diagnosed with AD (17 men, 48 women; age range, 46–87 years; mean age, 74.1 ± 7.8 years), 24 with FTD (13 men, 11 women; age range, 48–77 years; mean age, 61.8 ± 9.1 years), 26 with VaD (18 men, eight women; age range, 57–87 years; mean age, 73.4 ± 9.8 years), and 11 patients with DLB (three men, eight women; age range, 67–87 years; mean age, 62.9 ± 8.1 years). All patients with dementia had a dementia severity of 0.5 (suspicious) or 1 (mild) based on the CDR (Hughes et al., 1982). All patients underwent general physical and neurological examinations and extensive laboratory testing, including thyroid function tests, serum vitamin B12, and syphilis serology, to exclude other potential causes of dementia. All individuals and/or the nearest relative of the patient gave informed written consent.

The profile of each patient (age, sex, years of education, and years of disease duration) was recorded, and the CDR score was rated by the chief clinician.

2.3. Diagnosis

All patients with AD met the criteria for probable AD formulated by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s...
Table 1
Comparison between the original and the adapted versions of the ACE.

<table>
<thead>
<tr>
<th>Item</th>
<th>Original</th>
<th>Adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Year, season, date, day, month</td>
<td>Unchanged. appropriate Japanese year accepted as correct response</td>
</tr>
<tr>
<td>Attention/calc.</td>
<td>100-7 up to five subtractions saying “WORLD” backward</td>
<td>Unchanged.</td>
</tr>
<tr>
<td>Memory</td>
<td>Lenon, key, ball</td>
<td>Unchanged. Saying “fu-ji-no-ya-ma” backward</td>
</tr>
<tr>
<td>Remote memory</td>
<td>UK PM (current and previous)</td>
<td>Seven-word address of local relevance</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Letter “p” and animal</td>
<td>Japan (current and previous)</td>
</tr>
<tr>
<td>Naming</td>
<td>Pen, watch, giraffe, pig, crown, goat, camel, helicopter, kite, windmill,</td>
<td>Japan (opposition leader), US (President)</td>
</tr>
<tr>
<td>Language comprehension</td>
<td>Read and obey and 1-stage, 3-stage and complex grammar</td>
<td>Letter “Sa” and animal</td>
</tr>
<tr>
<td>Repetition</td>
<td>Brown, conversation, articulate</td>
<td>Unchanged.</td>
</tr>
<tr>
<td>Reading</td>
<td>Regular words</td>
<td>Replaced with Japanese words of comparable frequency and length</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>Overlapping pentagon, wire cube, clock-face drawing</td>
<td>Replaced with Japanese phrase of comparable complexity and length</td>
</tr>
</tbody>
</table>

2.5. Statistical analysis

Statistical analysis was performed using the SPSS 14.0 J software program (SPSS Inc., Chicago, IL, USA). A value of P<0.05 was accepted as significant.

3. Results

Table 2 summarizes the socio-demographic characteristics and scores on the ACE and MMSE for dementia and control groups in the complete sample.

Among the dementia group, the sensitivity and 1-specificity of the ACE and MMSE in diagnosing dementia was shown in the receiver operating characteristics (ROC) curve in Fig. 1. The area under the ROC curve (AUC) of the ACE was 0.987 and of the MMSE was 0.963.

Among the dementia group, the sensitivity and specificity for diagnosing FTD with a Verbal-Language/Orientation Memory (VLOM) ratio <2.2 was 16.7% and 96.1%, and the sensitivity and specificity for diagnosing AD with a VLOM ratio >3.2 was 84.6% and 60.7%.

4. Discussion

4.1. Japanese version of ACE

This study was performed to evaluate the Japanese version of the ACE in detecting early dementia. We compared the validity of the ACE measured in terms of internal consistency, using Cronbach’s alpha coefficient. The Cronbach’s alpha for the ACE was 0.82.

Two methods were used to calculate the norms for the composite score on the ACE. The first ACE cutoff score of 80/100 represented a value two standard deviations (S.D.s) below the mean composite score for the control group. The second cutoff was obtained by estimating the probability of diagnosing dementia in the 202 subjects in the clinic group. We estimated the sensitivity, specificity, and positive predictive values (PPVs) for diagnosing dementia at different prevalence rate (5, 19, 20, and 40%) for each ACE cutoff score from 70 to 80. A broad range of prevalence rates was chosen to encompass the wide variation reported in various studies. A cutoff of 80 had high sensitivity (98%) at a specificity of 87% (Table 3). A cutoff score of 74 had optimal sensitivity (89%) and specificity (99%), and maintained a reasonably high PPV at different prevalence rates. Table 3 also shows the sensitivity, specificity, and predictive values for diagnosing dementia using the MMSE with a conventional cutoff of 24 and a higher cutoff of 27 for the same sample population.

DSM-IV was used to estimate the criterion validity of the ACE (composite score) in diagnosing dementia. The trade-off between sensitivity and 1-specificity of the ACE and MMSE in diagnosing dementia is shown in the receiver operating characteristics (ROC) curve in Fig. 1. The area under the ROC curve (AUC) of the ACE was 0.987 and of the MMSE was 0.963.

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with the validity of the MMSE, which is a short test with widespread international usage. We compared the diagnostic accuracy of the tests not only with regard to sensitivity and specificity, but also with regard to AUC. The AUC is independent of the decision criteria and less contaminated by the external factors that affect the response (Alexopoulos et al., 2006). Thus, the AUC provides a better measure of predictive accuracy than the measurement’s sensitivity and specificity (Kim et al., 2005).

According to our findings, the Japanese ACE has excellent accuracy in differentiating between patients with early dementia and cognitively healthy participants. The ACE has good sensitivity and specificity in detecting early dementia. The AUC value of the ACE for identifying early dementia was 0.987. This value indicates excellent accuracy.

4.2. Difference between scores in the original ACE and Japanese ACE (Table 4)

The two cutoff values for the original ACE were 88 and 83 (Mathuranath et al., 2000), while those for the Japanese ACE composite were 80 and 74. Where does the difference come from? Table 4 summarizes the mean individual component and composite scores on the ACE for the cognitively normal groups of the original study and this study. Exact statistical analysis cannot be conducted, but the control group in this study had lower scores on memory and verbal components than the control group in the original study. Tests of both memory and verbal components include tests used language. The Indo-European languages including English are written in letters, whereas Japanese language is written in syllables. A “seven-word address” in the memory component of the Japanese version of the ACE might be more difficult than that in the original ACE. In the verbal fluency test also, the difference between letters and syllables might affect the results. In English, the alphabet consists of 26 letters, whereas in Japanese, the “kana” writing system consists of 46 syllables. The number of words beginning with letter “p” might be bigger than the number of words beginning with the syllable “sa”, and therefore, saying words beginning with the syllable “sa” might be a more difficult task than saying words beginning with the letter “p”.

4.3. VLOM ratio (Table 5)

We found that a VLOM ratio >3.2 indicated a better sensitivity in detecting AD than reported by Mathuranath et al. (84.6% versus 75%), but showed lower specificity (60.7% versus 84%) (Mathuranath et al., 2000) (Table 5).

The major discordant finding in this study is the complete failure of the ACE to detect FTD. In fact, only 16.7% of FTD cases had a VLOM ratio <2.2. Our result is in line with that of Bier et al. (2004). The VLOM ratio is the ratio between scores in language tasks and memory tasks. A lower VLOM ratio indicates a specific deficit in language rather than in memory functions. In our dementia group, we had no case of primary progressive aphasia or semantic dementia among our FTD patients, who all presented with the pure frontal form of the disease. We agree with the opinion of Bier et al. and think that a low (<2.2) VLOM ratio may be effective in diagnosing the forms of FTD with a selective language deficit.

4.4. Limitations of this study

Our study has several limitations. The participants were recruited at a university center. Thus, our results apply only to a clinic-based patient population. The applicability and reliability of the ACE in community samples require further investigation.

We used the clinical diagnosis based on a comprehensive diagnostic workup and on international diagnostic criteria as the gold standard. Despite the high validity of the diagnostic criteria, clinical diagnoses are not always confirmed at autopsy. Thus, we should take into account the possibility of erroneous clinical assessments. Therefore, the validity of the ACE may be lower than our results suggest.

5. Conclusion

The Japanese version of the ACE is a very accurate instrument for the detection of early dementia, and should be widely used in clinical practice.
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