Differentiation of semantic dementia and Alzheimer’s disease using the Addenbrooke’s Cognitive Examination (ACE)

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SUMMARY

Background The Addenbrooke’s Cognitive Examination (ACE) is a simple diagnostic tool bridging the gap between the very brief Mini Mental State Exam (MMSE) and much longer test batteries used by neuropsychologists which has proven extremely popular internationally.

Objective We aimed to assess the ability of the ACE to differentiate semantic dementia (SD) from Alzheimer’s disease (AD).

Methods The ACE was administered to three groups: SD patients (n = 40) and two separate groups of AD patients (n = 40 in each), matched for overall ACE or MMSE score.

Results Significant differences were found between SD and both AD groups for the ACE sub-scores of naming, reading and orientation in time. Discriminant analysis (SD versus AD) led to the formulation of a ‘semantic index’ (naming plus reading minus scores for serial-7s, orientation in time and drawing). Application of the semantic index to the patient data found values of less than zero to be predictive of SD rather than AD with 88% sensitivity and 90% specificity. Validation analysis in an independent sample of 24 SD and AD patients proved even more favourable.

Conclusions The overall ACE score is known to be a sensitive, and specific, indicator of early neurodegenerative dementia; this study shows that the ACE can also be used to detect SD through application of the semantic index.

INTRODUCTION

Several simple cognitive screening batteries have been devised for use in dementia patients. Such instruments aim to be brief, to cover a range of cognitive domains and to be relevant in different conditions. The Mini Mental State Exam (Folstein et al., 1975) is the most widely used and has advantages in brevity and ease of administration but lacks sensitivity (Feher et al., 1992). The Addenbrooke’s Cognitive Examination (ACE) (Mathuranath et al., 2000) was developed with the aim of providing clinicians with a simple diagnostic tool to bridge the gap between the MMSE and longer, comprehensive test batteries used in the evaluation of dementia (Mattis, 1988; Huppert et al., 1995). The 100-point ACE incorporates the MMSE but extends it to include tests of memory, language and executive function. It takes 10–15 min to administer and assesses six domains (orientation, attention, memory, verbal fluency, language and visuospatial function). It is more sensitive than the MMSE for the early detection of Alzheimer’s disease (AD) (Mathuranath et al., 2000), can distinguish depression from dementia (Dudas et al., 2005) and can differentiate neurodegenerative syndromes including AD, frontotemporal dementia (FTD) and the Parkinsonian disorders (Mathuranath et al., 2000; Bak et al., 2005). Versions are available in several languages (Bier et al., 2004; Mathuranath et al., 2004).
Semantic dementia (SD) is a syndrome that falls within the clinical spectrum of frontotemporal dementia (FTD) (Snowden et al., 1989; Hodges et al., 1992; Garrard and Hodges, 2000). It is characterised by progressive impairment in semantic memory (our permanent store of knowledge concerning objects, people, concepts and word-meanings) with relative preservation of memory for events (episodic memory) and of other cognitive domains. SD is associated with asymmetric anterior temporal lobe atrophy, involving the left more often than the right hemisphere (Thompson et al., 2003). Recent studies have confirmed that the clinical syndrome of SD is almost always associated with the form of FTD characterised by ubiquitin-positive neuronal inclusions (Rozors et al., 2000; Davies et al., 2005).

AD and SD form a double-dissociation: severely impaired semantic memory with relatively preserved episodic memory in SD and impaired episodic with preserved semantic memory in early AD (Hodges et al., 1992; Hodges and Patterson, 1995; Garrard and Hodges, 2000). Formal neuropsychological assessment easily detects the differing cognitive profiles but, for a number of reasons, brief clinical assessment may not. Firstly, patients with both AD and SD complain of poor 'memory' and word-finding difficulty. Furthermore, reliance on word-based tests to evaluate episodic memory produces misleading results because saliency of verbal stimuli is reduced in SD, giving low scores that are not the result of true amnesia (Seachill et al., 2005). Conventional neuroimaging may also fail to distinguish between AD and SD: CT may be unremarkable in both. MRI with coronal slices shows focal anterior/inferior temporal gyral atrophy in SD relative to AD, but MRI is not always available (Galton et al., 2001; Davies et al., 2004).

That SD is under-diagnosed, presumably mislabelled as AD, is suggested by the discrepancy between numbers of cases in specialist centres vs dementia services at large and also by the growing SD literature. Correct identification of dementing diseases is important for imparting information to patients and carers, and in selecting optimal pharmacotherapy. The original publication on the ACE included a comparison of AD and combined behaviour aphasis FTD group; this study assesses the diagnostic accuracy of the ACE specifically in differentiating between AD and SD.

METHODS

We reviewed 40 consecutive SD patients seen at the Memory Clinic between March 1997 and December 2003 to whom the ACE had been given. Scores from the first administration of the ACE were used. Nine patients had presented before the ACE was administered routinely to all clinic patients: their first ACE dated on average, 2.0 years (SD = 1.3) after presentation. Patients were diagnosed according to international consensus criteria (Neary et al., 1998; McKhann et al., 2001) based upon clinical interview, extensive standard neuropsychological testing, and the findings of asymmetric anterior temporal lobe atrophy on coronal MRI. It is important to note that ACE scores were not used to make the diagnosis. We compared the ACE-profile with that in two groups of 40 AD patients diagnosed using the NINCD-S-ADRDA criteria (McKhann et al., 1984). One AD group was matched for total ACE score and the other matched for MMSE score: both were matched for sex and, as closely as possible, for age. Diagnostic inferences drawn from this analysis were tested in a new group of 12 consecutive SD patients (and 12 ACE-matched AD patients) that presented between January 2004 and March 2005. The study was approved by the Cambridge Local Research Ethics Committee.

ACE testing items were grouped into twelve sub-scores: orientation in time (max = 5); orientation in place (max = 5); serial-7s (max = 5); verbal registration (three single-words and a seven-point name and address repeated three times, max = 24), verbal recall (three single-words and the seven-point address, max = 10), public knowledge (max = 4), lexical fluency (production of words commencing with P, max = 7), category fluency (production of animal names, max = 7); naming (simple line drawings, max = 12); reading (orthographically regular and irregular words, max = 2); other language (syntactic comprehension, repetition and sentence-writing, max = 14); and drawing (overlapping pentagons, wire cube and clock-face, max = 5). ACE sub-scores were compared across groups by t-tests with Bonferroni correction (SD vs ACE-matched AD, SD vs MMSE-matched AD). Discriminant analysis was performed with variables entered in a stepwise manner between the SD group and each AD group in turn.

On the basis of this analysis we devised a simple arithmetic formula, the 'semantic index', which was then used in receiver-operator characteristic (ROC) curve analyses [area under curve with 95% Confidence Interval (CI), sensitivity and specificity quoted]. An identical ROC analysis was then undertaken for validation purposes on the independent sample of new SD and matched AD patients. Statistics were performed in SPSS10 (SPSS Inc., Chicago, IL, USA).
RESULTS

The 40 SD patients included 25 men and 15 women and had a mean age of 62.9 ± 7.0 years. Their mean ACE and MMSE scores were 56.7 ± 20.3 and 22.9 ± 5.6, respectively. Both AD groups had the same numbers of men and women but were slightly older, in keeping with the known demographics of AD; the MMSE-matched group were aged 66.7 ± 8.8 years and the ACE-matched group were aged 67.2 ± 7.9 years (both differing significantly from SD, p < 0.05). Mean ACE score in the MMSE-matched group was 68.3 ± 19.9 and mean MMSE score in the ACE-matched group was 19.6 ± 6.2, indicating the latter to be at a more advanced stage of their illness (p < 0.05) (Table 1).

Comparison of ACE sub-scores between the SD cases and the two AD groups showed significantly worse scores in SD for ‘naming’ and ‘reading’ (p < 0.001 for both) and significantly worse scores in AD for orientation in time (p < 0.05) (Table 1). In addition, the MMSE-matched AD group scored significantly better than the SD group on letter and category fluency (p < 0.01, p < 0.001, respectively) and the ACE-matched AD group obtained significantly lower scores on serial-7s and drawing (p < 0.001 for both).

Discriminant analysis between SD and ACE-matched AD established the key variables as naming, reading, serial-7s, orientation in time and drawing (standardised discriminant coefficients of 0.75, 0.46, −0.48, −0.35 and −0.38, respectively; 94% of cases correctly classified). The parallel analysis between SD and MMSE-matched AD gave highly favourable values for the diagnostic utility of the semantic index, with area under curve of 0.96 (0.92–1.0) and 0.97 (0.93–1.0), respectively. Taking zero as the cut-off correctly classified 36 of the 40 SD cases and 70 of the 80 AD cases with a sensitivity of 88% and specificity of 90% (Table 2). Applying the semantic index to an independent sample of 12 newly diagnosed SD patients and ACE-matched AD patients provided striking confirmation of its diagnostic value with an area under ROC curve of 0.99 (0.95–1.0), sensitivity 92%, and specificity 100% for a zero cut-off (Figure 1, Table 3).

Table 1. Comparison of ACE sub-scores (mean ± standard deviation) in SD and matched AD groups

<table>
<thead>
<tr>
<th></th>
<th>SD</th>
<th>AD (ACE-matched)</th>
<th>AD (MMSE-matched)</th>
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</thead>
<tbody>
<tr>
<td>Orientation in place (max 5)</td>
<td>3.7 ± 1.6</td>
<td>3.9 ± 1.4</td>
<td>4.4 ± 1.1</td>
</tr>
<tr>
<td>Orientation in date (max 5)</td>
<td>3.7 ± 1.6</td>
<td>2.5 ± 1.7***</td>
<td>2.9 ± 1.6*</td>
</tr>
<tr>
<td>Serial-7s (max 5)</td>
<td>4.5 ± 1.2</td>
<td>2.6 ± 2.1***</td>
<td>3.7 ± 1.9</td>
</tr>
<tr>
<td>Registration (max 24)</td>
<td>15.2 ± 6.6</td>
<td>13.9 ± 6.9</td>
<td>17.1 ± 7.0</td>
</tr>
<tr>
<td>Verbal recall (max 10)</td>
<td>2.2 ± 3.0</td>
<td>1.8 ± 2.4</td>
<td>2.2 ± 2.8</td>
</tr>
<tr>
<td>Public knowledge (max 4)</td>
<td>0.8 ± 1.1</td>
<td>1.0 ± 1.2</td>
<td>1.3 ± 1.2</td>
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<tr>
<td>Letter fluency (max 7)</td>
<td>3.1 ± 1.7</td>
<td>3.4 ± 2.0</td>
<td>4.3 ± 2.0**</td>
</tr>
<tr>
<td>Category fluency (max 7)</td>
<td>2.0 ± 1.8</td>
<td>2.4 ± 1.7</td>
<td>3.5 ± 1.8***</td>
</tr>
<tr>
<td>Naming (max 12)</td>
<td>4.8 ± 4.2</td>
<td>9.7 ± 2.7***</td>
<td>10.8 ± 2.2***</td>
</tr>
<tr>
<td>Other language (max 14)</td>
<td>11.4 ± 2.8</td>
<td>11.6 ± 2.3</td>
<td>12.8 ± 2.0</td>
</tr>
<tr>
<td>Reading (max 2)</td>
<td>1.1 ± 0.5</td>
<td>1.6 ± 0.6***</td>
<td>1.8 ± 0.5***</td>
</tr>
<tr>
<td>Drawing (max 5)</td>
<td>3.9 ± 1.1</td>
<td>2.4 ± 1.9***</td>
<td>3.5 ± 1.7</td>
</tr>
<tr>
<td>Total MMSE score (max 30)</td>
<td>22.9 ± 5.6</td>
<td>19.6 ± 6.2*</td>
<td>22.9 ± 5.6</td>
</tr>
<tr>
<td>Total ACE score (max 100)</td>
<td>56.7 ± 20.3</td>
<td>56.7 ± 20.3</td>
<td>68.3 ± 19.9*</td>
</tr>
<tr>
<td>Semantic Index</td>
<td>−6.7 ± 4.7</td>
<td>3.8 ± 3.6***</td>
<td>2.5 ± 2.8***</td>
</tr>
</tbody>
</table>

*p < 0.05.
**p < 0.01.
***p < 0.001.
DISCUSSION

The ACE is a simple clinical tool increasingly used in the assessment of dementia (Mathuranath et al., 2000; Bak et al., 2005; Dudas et al., 2005). Total ACE score is known to be a reliable indicator of neurodegenerative dementia versus non-dementia (Mathuranath et al., 2000). This study shows that examination of the ACE profile in addition distinguishes reliably between SD and AD. Consideration of just five items from the ACE discriminated between SD and AD cases, defined on comprehensive multidisciplinary assessment, with sensitivity and specificity of about 90%.

The key ACE sub-scores in distinguishing SD from AD were naming, reading, serial-7s, orientation in time and drawing. Naming and reading were worse in SD: naming is the most exacting test of semantic memory while surface dyslexia (mispronunciation of irregularly spelt words, e.g. pint to rhyme with hint) is a consequence of semantic impairment (Hodges et al., 1992). Both letter fluency and category fluency were significantly worse in SD than MMSE-matched AD, but neither appeared in the discriminant analysis, presumably because their discriminating power was subsumed by the naming and reading scores. Numerical and visuo-spatial skills often become impaired in AD but are typically preserved in FTD (Hodges et al., 1992); this was borne out by the higher scores for serial-7s and drawing in SD. Orientation in time was also consistently worse in AD in keeping with impaired day-to-day memory being a core AD symptom (Welsh et al., 1992); memory for events, by contrast, often seems to be preserved in SD.

Interestingly, scores on the main word-based tests of attention and memory (verbal registration, verbal recall and orientation in place) were as low in SD as AD, but for different reasons. Patients with SD perform poorly on verbally based test of memory because of their degraded semantic knowledge. That is to say, they no longer fully understand the meaning of words used in such tests leading to poor encoding and retrieval (Hodges et al., 1992; Scahill et al., 2005). Similarly they are likely to fail place orientation questions due to either comprehensive or word production deficits. Scoring in SD was better on tests of attention and memory that were less challenging to the semantic system (serial-7s and orientation in time). General knowledge items, in theory, might have been easier in AD than SD but the difficulty of the task meant that scoring was near floor level in both syndromes. ‘Other language’ items in the ACE consist of a range of tests of syntactic comprehension and single-word repetition not typically impaired, at presentation, in either SD or AD.

Unsurprisingly, there was greater disparity between SD and the milder (MMSE-matched) AD group for the ‘semantic’ items in which scoring was generally better in AD. Numerical and visuo-spatial items, by contrast, in which performance was generally stronger in SD, showed greater disparity between SD and the more advanced (ACE-matched) AD group. The need to differentiate SD and AD at varying stages, reflecting varying severity at presentation, was captured by the discriminant analysis. The resulting ‘Semantic Index’ balanced semantic and visuo-spatial scores and, fortuitously, the memorable cut-off of zero gave
sensitivity and specificity of some 90% or greater in each of the three separate analysis undertaken (SD vs MMSE-matched AD, SD versus ACE-matched AD and new sample SD vs AD).

The semantic index represents an extension and refinement of the VLOM ratio described in the original validation of the ACE (Mathuranath et al., 2002) as a method to differentiate AD from FTD. The FTD group (n = 29) in the earlier study was relatively small and made up of a mixture of SD, progressive non-fluent aphasic and behavioural variant cases. Some subsequent authors have found the VLOM to have rather low specificity (Bier et al., 2004; Larner, 2005) which we suspect reflects the fact that their groups also encompassed behavioural and linguistic variants of FTD. By focusing on the SD form of FTD, the semantic index appears to have superior utility as demonstrated in the independent prospectively assessed subgroup in the study.

Since the completion of this study we have revised the ACE (Mioshi et al., 2006). The ACE-R appears to have equivalent psychometric properties to the original with more precise scoring criteria and greater ease of translation into other languages. We have not yet seen a sufficiently large numbers of new SD cases to validate the semantic index in the ACE-R but our clinical experience suggests that it is equally applicable as it contains all of the elements from which the semantic index is derived.

In conclusion, the ACE is highly sensitive to SD and careful observation of the profile of scores across the sub-components of the ACE, captured in the semantic index, can accurately differentiate SD from AD. It is helpful in alerting clinicians to the diagnosis of SD particularly when neuropsychological and MRI resources are limited.

CONFLICT OF INTEREST
None.

ACKNOWLEDGEMENTS
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REFERENCES


