Screening for Cognitive Dysfunction in Corticobasal Syndrome: Utility of Addenbrooke’s Cognitive Examination

Robert Mathew, Thomas H. Bak, John R. Hodges

Introduction: The motor features of corticobasal syndrome (CBS) are well recognized but the fact that many, if not all, affected patients develop cognitive impairment is still underrecognized. The dementia of CBS overlaps most with a language variant of frontotemporal dementia: progressive nonfluent aphasia (PNFA). The aim of this study was to determine the usefulness of Addenbrooke’s Cognitive Examination-Revised (ACE-R) in the evaluation of CBS and to document similarities and differences between CBS and PNFA.

Materials and Methods: Patients with well-defined CBS or PNFA from two tertiary referral centers were selected along with matched controls. Results: Twenty-one patients with CBS, 23 patients with PNFA and 47 age- and education-matched controls were included. Both CBS and PNFA groups showed substantial impairment on the ACE-R (f = 17.3–80.2, p < 0.001) and were significantly impaired in all domains (p < 0.001). The only significant difference between CBS and PNFA was in the visuospatial domain (p < 0.009), being worse in CBS. Using a cutoff of 88/89 out of 100, 90% of CBS and 82.6% of PNFA patients were impaired. At this cutoff of 88/89, ACE-R in CBS had sensitivity and specificity values of 91 and 98%, respectively.

Key Words
Addenbrooke's Cognitive Examination · Addenbrooke's Cognitive Examination-Revised · Corticobasal degeneration · Corticobasal syndrome · Progressive aphasia

Abstract
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of pathologies notably FTD with tau-positive inclusions and Alzheimer’s disease [6, 10].

Assessment of patients with potential CBS in the clinic should involve both motor and cognitive evaluation, yet the utility of screening instruments is uncertain. Although a number of studies have explored cognition and language in CBS using detailed neuropsychologic batteries, there is clearly a need for assessment tools that are brief but useful [2–4, 7, 11]. The Mini-Mental State Examination (MMSE), which has been widely used for the screening of dementia, has the advantage of brevity and ease of administration, but lacks sensitivity to frontal, linguistic, and early amnestic deficits. Addenbrooke’s Cognitive Examination (ACE) and its revision (ACE-R) are cognitive screening tests that incorporate the MMSE with expanded memory, language and visuospatial components, plus a test of verbal fluency [12, 13]. The ACE and ACE-R are able to detect early-stage dementia [12, 14] and have been shown to distinguish between FTD and Alzheimer’s disease, although this is not a universal finding [15, 16]. Of relevance to the present study the ACE appears appropriate for the detection and monitoring of progressive aphasia syndromes and is sensitive to impairment in both semantic dementia and PNFA [17, 18]. The ACE has also been applied to patients with parkinsonism syndromes [12, 19, 20]. The original ACE appears useful in CBS, but the revised version, which allows analysis of the pattern across domains, has not been applied to a substantial cohort of well-defined CBS patients [19, 20] and importantly there has been no direct comparison of CBS and PNFA.

The aim of this study was to determine the usefulness of ACE in the evaluation of CBS, and to explore appropriate cutoffs for detecting cognitive impairment. A second aim was to document similarities and differences between CBS and PNFA, and a third aim was to confirm previous reports regarding the profile of cognitive deficits in CBS.

Materials and Methods

The databases of two tertiary referral centers for cognitive and movement disorders were searched (FRONTIER, Fronto temporal Dementia Research Group in Sydney www.ftdrg.org, and DMC, Disorders of Movement and Cognition Clinic, Cambridge, UK) for cases assessed since the introduction of the ACE-R. All patients were assessed by one of two experienced neurologists (J.R.H. and T.H.B.) and underwent neurological examination, neuroimaging (CT or MRI) and standard neuropsychological assessments, and were followed up, whenever possible, until death. The diagnosis of CBS was made according to the criteria of Shelley et al. [5] and Bak and Hodges [21]. The diagnosis of PNFA was made according to the international consensus criteria for subtype of FTD [22, 23], on the basis of impaired motor speech and/or agrammatism with distorted hesitant and aprosodic speech output but sparing of semantics. The details of some of these patients have been described previously [18]. Matched healthy controls were selected from the FRONTIER database.

The ACE-R surveys key aspects of cognition without the use of specialized test equipment and compares five subscales: Attention and Orientation, Memory, Fluency, Language and Visuospatial. It takes an average of 15 min to complete [12, 13]. It is freely available in 15 languages with 7 more in development (see website http://www.ftdrg.org/).

Statistics

SPSS software for Windows version 18 was used. One-way ANOVA was used to compare mean scores between various groups. For uniformity ACE-R scores were converted to percentage of maximum score. The receiver operating characteristic (ROC) curve was used to explore the ability in diagnosing the disease at the time of presentation of various criteria. Likelihood ratio was calculated from the sensitivity and specificity values. One-sample t test was used to compare ACE-R subscores within each group.

Results

Twenty-one patients with CBS (age 68 ± 8 years), 23 patients with PNFA (age 68 ± 10 years) and 47 age- and education-matched controls (age 67 ± 4 years) were included in the study. The mean duration of illness of patients with CBS was 4 (SD 4.0) years and PNFA 1.7 (SD 0.9) years (table 1).

Both CBS and PNFA groups showed substantial impairment on the ACE-R. One-way ANOVAs revealed significant group effects for both the total score and subscores (f = 17.3–80.2, p < 0.001). Post hoc pairwise comparisons between groups showed that the CBS as well as the PNFA group were significantly impaired versus controls in all domains (p < 0.001). The only significant difference between CBS and PNFA was in the visuospatial subscore with the CBS group performing more poorly than the PNFA group (p < 0.009).

The magnitude of impairment across domains on the ACE-R is illustrated in figure 1. It can be seen that the most impaired domain in CBS was verbal fluency followed by visuospatial function and memory. Attention and orientation was the least involved. The profile in PNFA is essentially the same with the exception of visuospatial function.

Two methods were used to explore the sensitivity and specificity of the ACE-R in CBS. Using a cutoff score of 88/89, representing two standard deviations below the controls’ mean composite score, which also corresponds...
Second, sensitivity and specificity values of the ACE-R for detecting cognitive dysfunction at various cutoff scores were determined and ROC was constructed. For CBS patients versus controls, the area under the curve was 0.99 and asymptotic significance <0.001, thereby indicating excellent test utility. A cutoff value of 88/89 produced a sensitivity of 91% and a specificity of 98%, while at a cutoff score of 82/83 sensitivity was 71% and specificity was 100%. The corresponding values for PNFA were 91 and 94% (for cutoff of 88/89) and 83 and 100%, (for a cutoff of 82/83). Table 2 shows the sensitivity and specificity at various cutoff values of ACE-R for CBS and PNFA.

Likelihood ratios were calculated for several cutoff scores based on the sensitivity and specificity values. With descending cutoffs from 92 to 85 (being the lower limit, i.e. 92 = 92/93) the likelihood ratio rose from 7.8 to 40.8 (Table 2), which means that a score of 85 is 40 times more likely to come from a patient with CBS than from a control subject. The corresponding likelihood ratio scores for PNFA were 7.5 at a cutoff of 92/93 and 43.5 at 88/89. In differentiating CBS from PNFA, the utility was poor as evidenced by an area under the curve of 0.5 and asymptotic significance of 0.6.

### Discussion

This study, the first to compare directly CBS and PNFA, has confirmed equivalent levels of cognitive dysfunction in those overlapping disorders. Using a cutoff of 88/89, the ACE-R detected cognitive dysfunction in 90% of the CBS patients (sensitivity 91%, specificity 98% and likelihood ratio of 40). The subscore profile ACE-R was very similar in CBS and PNFA, except for poorer visuospatial function in CBS.

As discussed above, the CBS syndrome is now conceptualized as a mixed motor and cognitive disorder. The cognitive impairment in CBS includes language, frontal executive functions and memory abilities [2–4, 7, 11].
The predominant form of language impairment in CBS fits within the umbrella of nonfluent aphasia with a marked reduction in speech fluency with deficits in grammar and motor speech. The prevalence of aphasia in CBS varies across studies and depends to a large extent upon selection criteria and the sophistication of the language assessment undertaken [2, 24]. In this study the vast majority of the patients (90%) had cognitive impairment based upon the ACE-R, which adds to the increasing evidence of cognitive impairment in CBS [3, 7]. Predictably, verbal fluency was the domain most affected in keeping with prior reports [2, 24], although the dementia was generalized with impairment in all areas including visuospatial function. The latter discriminated CBS from PNFA.

The ACE, though initially devised as a screening instrument for Alzheimer's disease and FTD, has recently been shown to be useful in parkinsonian and progressive aphasic syndromes with an annual rate of change of 10 points per year in both PNFA and semantic dementia [18]. It is remarkable that patients presenting with an isolated language disorder, PNFA, and those with a syndrome originally conceptualized as a movement disorder sparing cognition, CBS, actually performed at a similar level on the ACE-R, further adding to evidence of overlap between these disorders that share the same range of underlying neuropathologies [6, 25]. The most notable difference was on the visuospatial component of the ACE-R. This domain includes copying of a pentagon and cube plus drawing a clock face, which may be compounded by impaired manual dexterity and, in addition, has two tests which are perceptually based (dot counting and fragmented letters) unaffected by apraxia. In summary, the ACE-R is sensitive to cognitive dysfunction in CBS with a very high level of impairment comparable to that found in patients with PNFA.

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### References


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**Table 2.** Likelihood ratios, sensitivity and specificity values at various ACE-R cutoff scores for CBS and PNFA versus controls

<table>
<thead>
<tr>
<th>ACE-R score</th>
<th>CBS vs. controls</th>
<th>PNFA vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sensitivity, %</td>
<td>specificity, %</td>
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<tr>
<td>82</td>
<td>71.4</td>
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<tr>
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<td>85.7</td>
<td>97.9</td>
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<tr>
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<td>100</td>
<td>87.2</td>
</tr>
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</table>

Likelihood ratio cannot be calculated as 1 – specificity is 0 (marked with an asterisk).