SHORT REPORT

Cognitive bedside assessment in atypical parkinsonian syndromes

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Background: Despite the growing recognition of the importance of cognitive symptoms for the diagnosis and management of atypical parkinsonian syndromes, the cognitive assessment of the patients in clinical practice often remains very limited.
Objectives: To examine the ability of a brief and simple cognitive screening test to detect cognitive deficits in atypical parkinsonian syndromes.
Methods: Addenbrooke's cognitive examination (ACE), the mini-mental state examination (MMSE), and the dementia rating scale (DRS) were applied to 26 patients with multiple system atrophy (MSA), 39 with progressive supranuclear palsy (PSP), and 25 with corticobasal degeneration (CBD). The results were then compared with those obtained in 30 healthy age matched volunteers and 30 patients with Alzheimer's disease.
Results: In all four diseases the rate of detection of cognitive impairment on ACE was higher than on MMSE and comparable with DRS. The severity of cognitive impairment was most pronounced in the CBD group, which showed a similar degree of impairment to the Alzheimer group. In contrast, MSA patients were the least cognitively impaired. The PSP group took an intermediate position.
Conclusions: Cognitive impairment in atypical parkinsonian syndromes can be detected using a brief and clinically applicable bedside test such as ACE.

Various screening batteries have been developed to detect cognitive decline in neurological diseases. Ideally, such an instrument should be brief, easy to administer and evaluate, cover a wide range of cognitive functions, and be applicable to different diseases. Unfortunately, a wide gap has developed between the brief cognitive screening tests and the much longer comprehensive test batteries applied by neuropsychologists in the formal evaluation of dementias. The test most widely used in clinical practice, the mini-mental state examination (MMSE),[1] has the advantage of brevity and ease of administration but lacks sensitivity to frontal, linguistic, and early mnestic deficits.[2] In contrast, the more comprehensive dementia rating sale (DRS)[3] has been successfully applied in a range of conditions including subcortical diseases such as Parkinson's disease, multiple system atrophy (MSA), and progressive supranuclear palsy (PSP).[4] Its use in everyday practice has, however, been limited by its length and by the need for specialised testing material.

The Addenbrooke's cognitive examination (ACE)[5] was developed with the aim of offering clinicians a brief and simple cognitive screening battery incorporating the MMSE but extending it to cover a wider range of cognitive domains including language and frontal-executive functions. It consists of six subtests assessing orientation, attention, verbal fluency, memory, language, and visuospatial function. It is more sensitive and reliable than the MMSE for early detection of dementia in Alzheimer's disease and frontotemporal dementia.[5] The ACE has not, however, been compared with comprehensive batteries such as the DRS or applied to diseases associated with predominantly subcortical pathology, such as atypical parkinsonian syndromes. Our aim in the present study was therefore to compare the ability of three screening instruments (MMSE, ACE, and DRS) to detect cognitive dysfunction in three atypical parkinsonian syndromes (PSP, MSA, and CBD).

METHODS

Ninety patients with atypical parkinsonian syndromes were assessed between 1996 and 2003 at Addenbrooke's Hospital, Cambridge. The assessment took place on their first visit and was part of a prospective study of cognition in movement disorders. Twenty six were diagnosed as MSA[6] (mean (SD) age 65 (7.2) years; length of education 10.8 (2.0) years), 39 as PSP[7] (age 69.2 (5.8) years; length of education 10.8 (2.5) years), and 25 as CBD[8] (age 67.1 (7.5) years; length of education 11 (2.5) years). Thirty Alzheimer's disease patients[9] (age 69.3 (8.3) years; length of education 11.9 (3.1) years) were recruited through the Cambridge Memory Clinic. Thirty healthy controls were recruited from the MRC-CBU control panel, consisting of two equivalent subgroups: one for the ACE (control 1, age 71.3 (5.5) years; length of education 11.2 (2.7) years); the other for the DRS (control 2, age 70 (1.8) years; length of education 11.2 (2.7) years). There were no significant differences in age and education between the patient and control groups. The ACE incorporates the MMSE and includes the following subsections: memory (learning and recall of a name and address, recall of names of famous people), orientation, verbal fluency (animals and words beginning with P), language (naming, comprehension, reading and writing), and visuospatial function (copy of pentagons, cube, and clock drawing). The time taken to administer the ACE (median 15 minutes) was significantly shorter than that needed to complete the DRS (median 25 minutes; paired *t* test, $p<0.001$).

RESULTS

Groups were compared using one way analysis of variance (ANOVA). Significant group effects ($p<0.001$) were found for the three tests ($F = 19.7$ for the MMSE, 18.0 for the DRS, and 24.5 for the ACE). A post hoc analysis revealed that the PSP, CBD, and Alzheimer's disease groups, but not the MSA group, were significantly impaired in relation to controls on all three tests. We next compared the diagnostic sensitivity of

Abbreviations: ACE, Addenbrooke's cognitive examination; CBD, corticobasal degeneration; DRS, dementia rating scale; MMSE, mini-mental state examination; MSA, multiple system atrophy; PSP, progressive supranuclear palsy

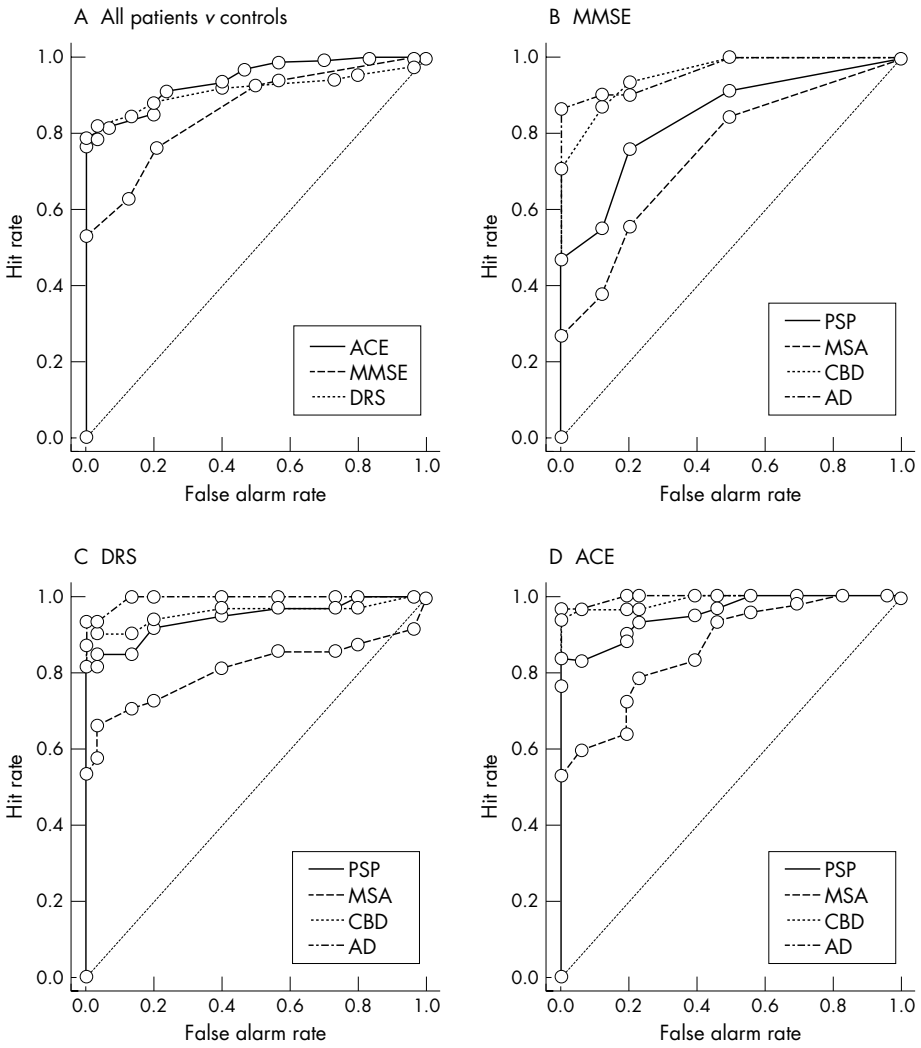

Figure 1 Receiver operating characteristic (ROC) curves for the three tests and different patient groups. (A) ROC curves for discriminating all patients from controls, for the three different tests. (B–D) ROC curves from the mini-mental state examination (MMSE), dementia rating scale (DRS), and Addenbrooke's cognitive examination (ACE), respectively, discriminating each of the four groups from controls.

the different tests, first for all patient groups considered together (fig 1, panel A), and then for each patient group separately (fig 1, panels B to D); these receiver operating characteristic (ROC) curves plot the hit rate (proportion of patients correctly classified as impaired) against the false alarm rate (controls incorrectly classified as impaired) for every possible threshold in each test. The more steeply bowed the curve, the better the test discriminates patient and control groups. Figure 1A shows the ROC curves for discriminating all patients from the healthy controls, for each of the three tests. Both ACE and DRS were found to be very sensitive: the correct detection rate approached 80% without risk of incorrect diagnosis among controls. MMSE performed more poorly overall: a comparatively large proportion of false positives was observed for detection rates exceeding 50%. The results indicate that, regardless of where the threshold for cognitive impairment is set, the MMSE is less sensitive than either the ACE or the DRS. With conservative thresholds, many patients will be missed; but with stricter thresholds, healthy controls will be misdiagnosed as impaired.

Panels B to D in fig 1 show how the ROC curves for the different tests vary across the four disease groups. The MMSE performed relatively well for the Alzheimer's disease group, detecting 85% of cases correctly without risk of false positive results. It did less well for the CBD group (false positives observed for hit rates exceeding 75%), and considerably worse for the PSP and MSA groups. The ACE and DRS performed comparably well for all disease groups.

These qualitative observations were confirmed quantitatively by computing discriminability indices for each of the curves in fig 1. The d'_a[10] indicates the distance between the population means in units equal to the root mean square standard deviation (an estimate of the pooled variance of the two populations). We also estimated the area under the ROC curve (A_z), a more intuitive measure of discriminability. When performance is at chance, the ROC curve is a straight line, indicated by the thin dotted line in each panel of fig 1, and the area under the curve is 0.5. With perfect discriminability, there are no false positives and a hit rate of 1.0, so the area under the curve is 1.0. A_z thus ranges from 0.5 to 1.0, with figures approaching 1 indicating that the measure has greater sensitivity. The two indices for each test and patient group are shown in table 1.

Comparison of both statistics for the three tests bears out the qualitative interpretation of the data: in all cases, both d'a and Az are considerably larger for the ACE and the DRS than for the MMSE. Thus the ACE appears to be as sensitive

Table 1 Discriminability indices for the different tests and patient groups

		MMSE	DRS	ACE
All patients	d'_a	1.49	1.93	2.10
	A_z	0.80	0.91	0.93
PSP	d'_a	1.38	2.18	2.20
	A_z	0.78	0.93	0.94
MSA	d'_a	0.96	1.19	1.48
	A_z	0.65	0.78	0.84
CBD	d'_a	2.28	2.38	2.61
	A_z	0.93	0.95	0.98
	d'_a	1.81	2.12	NA
Alzheimer's disease	A_z	0.95	0.99	0.99

Note: there were too few points on the ROC curve for which the hit rate was less than 1, and the false alarm rate greater than 0, to calculate d'_a in this cell.
ACE, Addenbrooke's cognitive examination; CBD, corticobasal degeneration; DRS, dementia rating scale; MMSE, mini-mental state examination; MSA, multiple system atrophy; NA, not assessed; PSP, progressive supranuclear palsy.

as the DRS for detecting cognitive impairment in Alzheimer's disease and in the subcortical syndromes.

Finally, the ROC analysis indicates that quite strict thresholds may be employed for all three tests without great risk of false diagnosis among healthy controls. No false positives were observed for a threshold as high as 88/100 in the ACE, 134/144 in the DRS, and 26/30 in the MMSE, cut off points corresponding fairly well to the highest thresholds employed in common practice.

DISCUSSION

In comparison with an established brief mental test (MMSE) and a comprehensive cognitive screening test (DRS), the ACE has proved to be an appropriate instrument to detect cognitive deficits in the four disease groups examined. In all four diseases the MMSE was the least sensitive test to discriminate patients from controls, as indicated by the results of the ROC analysis. The comparison of sensitivity for different patient groups indicated that the MMSE is especially insensitive to cognitive impairment in subcortical syndromes. It is important to note that increasing the MMSE threshold will not improve its diagnostic sensitivity. While strict cut off values may yield a modest improvement in detection rate, they will also produce false positive results in healthy controls while still failing to capture subtle cognitive dysfunction apparent in the parkinsonian patients. In contrast, both the ACE and DRS proved to be more accurate and robust instruments for distinguishing the patients from the controls. The ROC analysis suggests that the use of comparatively high thresholds in both tests will improve the detection rate of cognitive impairment without risk of increased false positive results (controls diagnosed as impaired).

The finding of a more profound cognitive deficit in PSP than in MSA gives support to the view that both diseases, despite the similarities in their clinical presentation, differ significantly in the involvement of cognitive functions.[11 12] Interestingly, the greatest degree of cognitive involvement was observed in the CBD group, supporting the recent reinterpretation of CBD as a cognitive as well as a motor disorder.[13 14]

Our results show that the ACE can be applied as a useful tool for cognitive screening. While the DRS remains an extremely valuable tool in neuropsychological research, we see the main purpose of the ACE to be in the cognitive bedside assessment of patients with dementias as well as movement disorders.

Addendum

Free copies of the ACE can be obtained from the corresponding author, who can also advise on the current state of the translations and adaptions into other languages (currently available in Spanish, Portuguese, Malayalam, and Hebrew). The MMSE part is subject to the copyright of PAR Inc (www.parinc.com).

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