

Application of Addenbrooke's Cognitive Examination to Diagnosis and Monitoring of Progressive Primary Aphasia

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Key Words

Dementia progression · Primary progressive aphasia · Semantic dementia · Addenbrooke's cognitive examination · Progressive nonfluent aphasia

Abstract

Background/Aims: Primary progressive aphasia (PPA) comprises 2 main variants: semantic dementia (SD) and progressive nonfluent aphasia (PNFA). Addenbrooke's Cognitive Examination (ACE) has become widely used for the diagnosis of dementias. Less information, however, is available about its ability to detect and monitor changes in cognition in PPA. We aimed to analyse the sensitivity and longitudinal changes of ACE scores in 2 subforms of PPA. **Methods:** We included 63 SD and 45 PNFA cases, all of whom had at least 2 assessments. Sensitivity levels, annualised rates of change and difference in scores over time on repeated ACE measurements were calculated. **Results:** A cut-off of 88 points detected 95% of the PNFA and SD cases. Longitudinal analysis showed an average annual decline of 10 points per year, with no significant difference between groups. **Conclusion:** The ACE is a useful tool for detecting and tracking the evolution of PPA.

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Introduction

Frontotemporal dementia (FTD), the term now preferred to describe patients with progressive atrophy involving frontal and/or anterior temporal regions of the brain, is the second commonest cause of younger-onset dementia [1]. Within FTD, 2 broad divisions are recognised: behavioural variant (bv-FTD) and primary progressive aphasia (PPA) [2, 3]. The latter is characterised by a relatively isolated language involvement in the first 2 years of evolution [4]. Based on the features of language impairment, semantic dementia (SD) and progressive nonfluent aphasia (PNFA) can be further distinguished [3, 5]. The former is characterised by a gradual dissolution of semantic memory, producing anomia and word comprehension deficits with preservation of grammar and phonological components of language [6]. In contrast, PNFA cases present with disturbances in motor aspects of language production and a variable degree of agrammatism but sparing of semantics [5, 7, 8]. A third variant of PPA in which neither PNFA nor SD criteria are fulfilled has become recently recognised as logopenic/phonological aphasia [9, 10]. This is characterised by paucity of speech and severe word finding difficulties, lack of apraxia of speech or agrammatism, difficulties in repetition of strings of words or sentences, and impairment of sentence comprehension.

These variants have been associated with different cortical involvement and underlying pathology [5, 9, 11, 12]. For instance, SD is strongly associated with tau-negative ubiquitin (TDP-43)-positive histology [13], whereas PNFA is largely related to tau-positive ubiquitin-negative pathology [5]. Finally, logopenic/phonological aphasia cases have been associated with Alzheimer's disease pathology [14]. Given the clinical and pathological heterogeneity, PPA variants might be expected to show different evolution and prognosis, but little is known about the longitudinal course of these syndromes.

A major goal in research on neurodegenerative disorders is the development of disease-modifying therapies targeted at the specific proteinopathies underlying the clinical syndrome. Such therapies are now undergoing early-stage trials in humans [15, 16]. Fundamental to large-scale trials will be the ability to assess changes over time. Although numerous language-based tests are available, these require specialist training for their administration and interpretation [17]. There is clear need for simpler and relatively quick assessment batteries capable of detecting and monitoring PPA syndromes.

The Addenbrooke Cognitive Examination (ACE) is a global cognitive bedside test that incorporates the widely used and validated Mini-Mental State Examination (MMSE) [18] with expanded memory, language and visuospatial components, plus a test of verbal fluency [19, 20]. The ACE is able to detect early stages of dementia [19, 21] and distinguishes reliably between frontotemporal dementia (FTD) and Alzheimer's disease [19, 22, 23] as well as other conditions such as affective disorders [24]. It has been adopted in >40 countries and is freely available in different languages (see website <http://www.ftdrg.org/>).

The aims of this study were to examine the usefulness of the ACE in the detection and monitoring of PPA. In particular, we wanted to compare SD and PNFA to see if there is a differential rate of decline and whether the ACE is sensitive to change over time.

Materials and Methods

Participants

We searched the databases of 2 specialist centres dedicated to FTD clinics [Cambridge Early-Onset Dementia Clinic and FRONTIER (Frontotemporal Dementia Research Group)] for cases assessed since the introduction of the ACE.

Only cases with 2 assessments on the ACE with at least 3 months between the first and last observations were included. Participants where English was not the first language or whose

baseline ACE scored <10 were excluded. A total of 108 cases were included: 63 with SD and 45 with PNFA.

The diagnosis was made according to the international consensus criteria for subtype of FTD [2, 3] and based upon a clinical assessment performed by an experienced clinician (J.R.H.), which included complete history and neurologic examination, plus comprehensive neuropsychological testing and magnetic resonance brain imaging. The core neuropsychological battery utilised in the majority of cases has changed over the years of the study but has always included tests of attention, executive functions, episodic memory, visuospatial processing, semantic knowledge and syntactic comprehension. It has been described previously elsewhere [7, 25]. Scores on the ACE were not used to classify cases.

Analysis

The original ACE [19] was introduced in 1997 and was replaced by the revised version (ACE-R) in 2006 [20]. To maximise the number of available cases we used scores from both versions. A subset of participants undertook both the original and revised versions. The scores of the 2 versions were highly correlated ($r = 0.97$, $n = 67$, $p < 0.01$, 2-tailed). A linear regression model identified a simple formula to make both versions comparable:

total score (revised version) = total score (original version) \times 0.931 + 6.977.

In order to evaluate ACE changes, we used 3 approaches:

(A) The annualised rates of change in total ACE scores were calculated in all cases according to the following formula reported by Rascovsky et al. [26]:

$$\text{ARC of ACE} = \left[\frac{\text{last ACE score} - \text{baseline ACE score}}{\text{months between evaluation}} \right] \times 12$$

(B) The second approach estimated the differences in total ACE scores over time. This was calculated by subtracting the last scores from the baseline ACE scores and then grouping according to 4 intertest intervals: 3–11 months, 12–23 months, 24–35 months and 36–48 months. All PPA cases were included.

(C) Finally, in order to reduce the individual differences and assess accurately changes within participants, repeated-measurement analysis was undertaken in the cases who presented 3 yearly observations. Therefore, 36 participants (27 with SD and 9 with PNFA) were available to compare the baseline with the first- and second-year scores.

Normal distribution of variables was confirmed via Kolmogorov-Smirnov test. χ^2 tests were used to compare categorical variables. For normally distributed numerical variables, the t test for independent samples was used. Otherwise, the Mann-Whitney U test was employed.

Analysis of covariance, adjusting for effect of baseline ACE scores, was undertaken to examine the impact of subtype of PPA and intertest intervals (approach B), whereas a mixed between-within subjects analysis of variance (repeated-measurement ANOVA) was carried out to assess the impact of either SD or PNFA on total ACE score changes across the baseline, first- and second-year observations (approach C). Statistical significance was set at the $p < 0.05$ level. Statistical analyses were undertaken using the Statistical Package for Social Sciences 17.0 for Mac (SPSS Inc., Chicago, Ill., USA).

Table 1. General features of the sample

	SD (n = 63)	PNFA (n = 45)	p value
Women, %	70.3	60.7	0.715 ^a
Mean age at initial visit, years	63.1 ± 7.41	67.1 ± 7.23	<0.05 ^b
Mean baseline total ACE score	60.0 ± 18.26	59.5 ± 22.23	0.915 ^b
Mean intertest interval, years	2.4 ± 1.72	1.6 ± 1.20	<0.05 ^c

Figures are means ± SD.
^a χ^2 test; ^b t test for equality of means (2-tailed); ^c Mann-Whitney U test (2-tailed).

Results

As table 1 shows, there were no differences between SD and PNFA cases in gender distribution or baseline ACE scores. Significant differences, however, were found for mean age and time of follow-up: SD participants were on average 4 years younger and had a longer mean follow-up. There was no correlation between baseline ACE scores and age of participants ($r = -0.032$, $p = 0.743$, 2-tailed).

The distribution of ACE scores when first assessed is shown in figure 1. It can be seen that sensitivity of ACE at a cut-off of 88, which is the level recommended for use in clinical settings [19, 27], was around 95% for both sub-forms, whereas at the lower cut-off of 82, the sensitivity was 90 and 78% for SD and PNFA cases, respectively. This asymmetrical proportion, however, was not statistically significant ($\chi^2 = 3.35$, d.f. = 1, $p = 0.067$).

The Annualised Rate of Change

The annualized rate of change was greater for PNFA (-11.2) compared to SD (-9.6), but this difference failed to reach statistical significance ($t = 0.66$, $p = 0.51$, 2-tailed). This variable did not correlate with age ($r = -0.008$, $n = 108$, $p = 0.932$, 2-tailed) or baseline mean ACE score ($r = -0.11$, $n = 108$, $p = 0.28$, 2-tailed).

Change in ACE over Time

The mean differences in total ACE scores by time epoch in the 2 subtypes of PPA are depicted in figure 2. An analysis of covariance showed a main effect of time [$F(3, 99) = 9.623$, $p < 0.001$], but there was no main effect of PPA subtype [$F(1, 99) = 0.550$, $p = 0.460$] or interaction of time by group [$F(3, 99) = 0.707$, $p = 0.550$], suggesting that the 2 groups decline to an equivalent degree. The

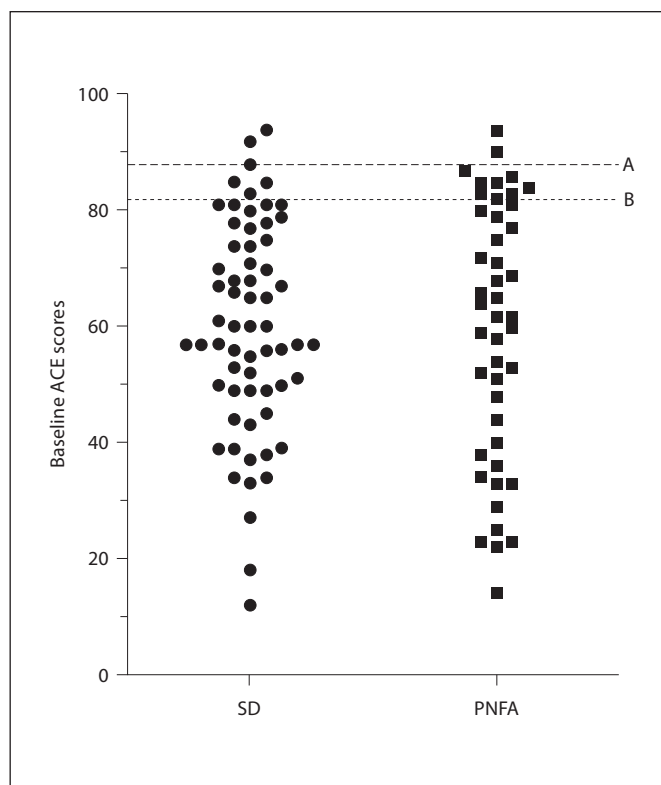


Fig. 1. Distribution of ACE scores at initial baseline assessment in the SD and PNFA groups. The dashed lines A and B represent the cut-off scores of 88 and 82 points, respectively ($n = 108$).

analysis of covariant baseline ACE score did not show a significant interaction [$F(1, 99) = 3.325$, $p = 0.071$]. Further pair-wise analysis, comparing ACE mean score changes and intertest intervals, showed no differences between contiguous intertest intervals except between the second and third periods. Noncontiguous intervals showed significant differences (see fig. 2).

Change in Individual Subjects

Figure 3 depicts the change in ACE scores of subjects with repeated assessments over 3 years. An analysis again demonstrated a substantial main effect for each time interval [Wilks' $\lambda = 0.526$, $F(2, 33) = 14.882$, $p < 0.01$] in both subgroups. There was, however, no significant subgroup effect [$F(1, 34) = 0.219$, $p = 0.643$] or interaction of time by group [Wilks' $\lambda = 0.968$, $F(2, 33) = 0.546$, $p = 0.584$], again pointing to an equivalent degree of change across the subgroups.

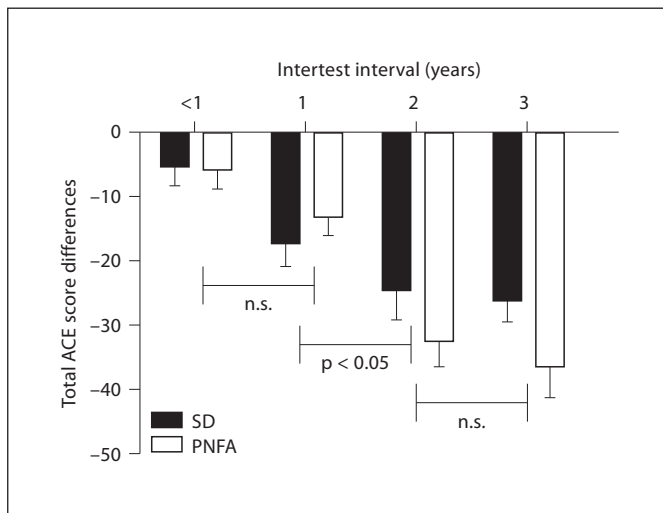


Fig. 2. Change in ACE score according to intertest interval in the SD and PNFA groups (n = 108).

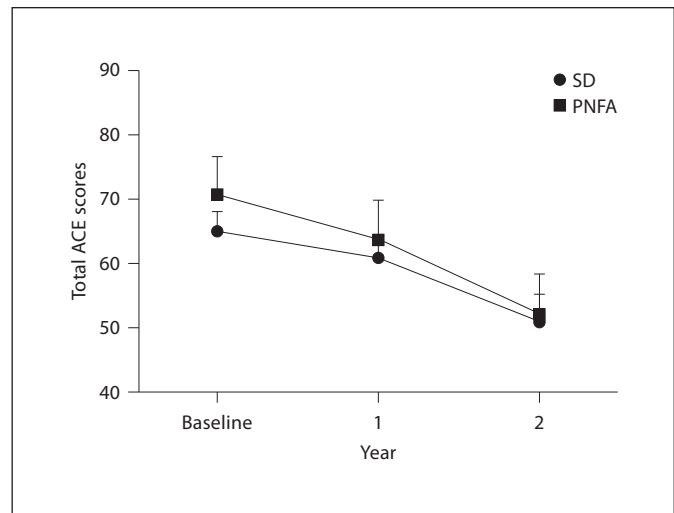


Fig. 3. Change in ACE scores in the cases with annual repeated assessments (n = 36).

Discussion

In keeping with our primary aims, we have shown that the ACE is sensitive to PNFA and SD subforms of PPA and able to detect cognitive changes over time, which appear to be equivalent in both subforms.

The ACE has previously been shown to be sensitive to the cognitive deficits found in SD [23], making it a valuable screening tool, although there have been no prior reports of its applicability in PNFA. In studies describing the ACE, a cut-off of 88 has been recommended for use in a clinic population to provide high sensitivity [19, 20, 27]. Using this cut-off, the sensitivity for PNFA and SD was 0.95. This means that only 5% of the cases would be missed using this threshold. At the lower cut-off of 82, the sensitivity for PNFA fell to 0.78, which is lower than for SD [20]. This may be explained by a greater impairment of semantic nonverbal tasks [28] and verbally mediated tasks in SD cases [29]. While semantically mediated tasks are prominent in the ACE (naming, word comprehension and animal fluency), the components sensitive to other aspects of language dissolution are more limited (word and phrase repetition, letter fluency). Subtle semantic deficits may, therefore, be detected more readily than syntactic and/or phonological problems [20]. The ACE should form part of the evaluation of suspected PPA, which also requires qualitative assessment of speech output.

Our study, as others [30–32], showed that SD patients were significantly younger than PNFA patients. This dif-

ference, however, was small, no more than 5 years, and the mean age did not exceed 70 in either group. Moreover, there was no significant correlation between age and either baseline ACE scores or annualised rate of change of ACE scores. Age, therefore, appears to have little impact on the level of ACE score decline over time.

In comparison with other dementias, SD, and in particular PNFA patients, show less functional impact in daily activities even when patients present at an advanced level of aphasia [33]. Consequently, the ACE may be suitable not only to detect initial cases but also to track the cognitive progression of PPA. This is particularly important in the context of clinical trials and other treatment interventions.

Regardless of the methods of analysis, we found an average fall of 10 points by year. Although there was a trend of more rapid decline in the PNFA group, none of the methodological approaches demonstrated any meaningful difference between the groups, which concurs with a longitudinal pathological based study that showed an undifferentiated decline in global cognition assessed by the MMSE [34]. A similar finding was reported in a longitudinal study in which changes in ACE scores in a year were comparable between subforms of FTD [35]. The same study, however, showed greater functional decline in the PNFA than in the SD. Moreover, another prospective study found a more rapid progression and shorter survival in nonfluent cases [36]. It is not clear whether this difference is due to a relatively later detection of PNFA

cases so that they present with a larger pathological burden at the time of diagnosis, or if they may actually have a more aggressive disease as suggested by some imaging studies [37].

Knowing the average rate of change in these syndromes is of value, especially when managing individual families to whom the question of the rate of change and likely prognosis is extremely relevant. The change over 12 or 24 months in an individual case can be put in the context of the average for that disorder.

Longitudinal studies of this type present a considerable methodological challenge, and there is clearly room for improvement in future studies. It would be of value to examine the relationship between changes in the ACE and functional decline in both PNFA and SD, incorporating both functional and cognitive measurements, and more individuals. Since this work began, logopenic/phonological aphasia has emerged as a clear clinicopathological entity. Consequently, our PNFA group almost certainly includes patients who now would be labelled as logopenic and future studies should obviously subdivide the nonfluent group.

Another limitation of this study is the lack of pathological confirmation, which remains the gold standard for diagnosis. Finally, it would be useful to include other variables in our analysis, such as length of disease.

In spite of these potential limitations, the ACE has clear advantages. It has fewer ceiling effects than other widely used screening brief instruments, such as the MMSE, making it more suitable for longitudinal studies. While other short bedside tests such as the Frontal Assessment Battery [38] focus purely on executive and behavioural aspects, the ACE has a broader diagnostic usefulness because of its substantial proportion of language tasks.

In summary, we have shown that the ACE is useful in the detection and monitoring of patients with focal dementia syndromes presenting with progressive aphasia. Very few cases of SD or PNFA would be missed using the upper cut-off of 88 on the ACE.

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