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## The Utility of the Addenbrooke's Cognitive Examination Version Three (ACE-III) in Early Onset Dementia

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**Running Title:** The Utility of ACE-III in Early Onset Dementia

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- Subjective memory complaints,
- Screening for cognitive impairment

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### ABSTRACT

**Backgrounds** Early onset dementia (EOD) is defined as functionally relevant cognitive decline with age of onset less than 65 years. The aim of this study was to investigate the utility of the recently validated third version of the Addenbrooke's Cognitive Examination (ACE-III) in predicting dementia diagnoses in EOD. **Methods** ACE-III scores of EOD patients were compared to those of healthy controls (HC) and individuals with subjective memory impairment (SMI). **Results** The study included 71 EOD patients: Alzheimer's disease (n=31); Primary Progressive Aphasia (n=11), behavioural-variant frontotemporal dementia (bvFTD, n=18); and Posterior Cortical Atrophy (n=11), 28 HC, and 15 SMI. At a cut-off score of 88/100, the ACE-III displayed high sensitivity and specificity in distinguishing EOD from HC (91.5% and 96.4%) and SMI (91.5% and 86.7%). **Conclusions** The ACE-III is a reliable cognitive screening tool in EOD.

## **INTRODUCTION**

Early onset dementia (EOD) is defined as functionally impairing cognitive decline arising before the age of 65 years.<sup>1</sup> Aetiologies are diverse; although the most common presentations are secondary to Alzheimer's disease, and frontotemporal dementia. Subjective cognitive impairment, relating to heightened awareness of normal symptoms or health-related anxiety, is an important differential diagnosis.<sup>2</sup>

Early and accurate diagnosis of dementia reduces uncertainty and unnecessary investigations, and allows more accurate prognostication. Crucially, it also facilitates timely introduction of symptomatic therapies and recruitment of well-characterised patients into clinical trials.<sup>3</sup>

The Addenbrooke's Cognitive Examination (ACE) is a cognitive test widely used for diagnostic screening, and longitudinal follow-up of cognitive decline in dementia. A third version of this tool (ACE-III) was designed to address weaknesses identified in previous versions and has been validated.<sup>4</sup> The instrument's utility has been recently investigated in patients over 75.<sup>5</sup> This study aimed to investigate the diagnostic utility of the ACE-III in EOD.

## **METHODS**

Patients with EOD were identified from the Edinburgh Cognitive Disorders Clinic Diagnosis Audit Research and Treatment (CDC-DART) Register at the Anne Rowling Regenerative Neurology Clinic, University of Edinburgh. We identified 71 consecutive patients fulfilling consensus clinical diagnostic criteria for specific dementia diagnoses,<sup>6-8</sup> including, Alzheimer's disease (AD, n=31), behavioural-variant frontotemporal dementia (bvFTD, n=18), primary progressive aphasia (PPA, n=11) and posterior cortical atrophy (PCA, n=11) presenting between December 2013 and December 2014. We also identified patients

attending the clinic with subjective memory impairment (SMI, n=15). Diagnoses were made following multi-professional clinical assessments (neurology, psychiatry, neuropsychology) incorporating where appropriate cerebrospinal fluid biomarkers and neuroimaging. The majority of patients (90.3%) had both structural (1.5T MRI, or CT if MRI contraindicated/not tolerated) and <sup>99m</sup>Tc-HMPAO SPECT brain imaging as part of routine evaluation.<sup>9</sup> SMI was defined as the presence of non-progressive symptoms (including on longitudinal follow up) whereby degenerative dementias have been excluded in the context of a high index of suspicion by a psychiatrist and neurologist that symptoms represent a heightened awareness of normal bodily symptoms or related to affective symptoms..

Patients were excluded if age at onset was older than 65, if a non-neurodegenerative cause for cognitive impairment was identified, or if there was diagnostic uncertainty.

ACE-III was conducted as part of routine clinical workup for all patients. The ACE-III was also undertaken in a cohort of healthy controls (n=28) recruited from the University of Edinburgh Department of Psychology research subject pool.

All participants gave informed consent for their data to be used for research as part of the CDC-DART register (approved by the Scotland-A Research Ethics committee). Recruitment of healthy controls was approved by the Department of Psychology, University of Edinburgh Ethics Committee.

## **STATISTICAL METHODS**

Between-groups comparisons were carried out using one-way-ANOVA with post- hoc Bonferroni-corrected pairwise comparisons. Standard methods were used to transform variables in case of non-normality. Proportions were expressed in percentages and comparisons were made using Pearson  $\chi^2$  test.

Correlational analyses were carried out using Spearman Rank correlation coefficient.

Receiver operating characteristic curve (ROC) analyses was used to identify optimum ACE-III cut-off to distinguish patients from controls.

All data was analysed using SPSS statistics (version 21). Cut-off for statistical significance was set at 0.05.

## RESULTS

### Comparison of ACE-III performance in patients with EOD and controls

There were no significant differences in baseline demographics between patients and healthy controls (HC) or between the dementia subgroups (see Table-1). SMI was associated with a significantly younger age compared to HC and EOD ( $p < 0.0001$ ) but there were no significant differences in sex distribution or education.

There was no significant correlation between ACE-III scores in EOD and disease duration or age. A ROC curve analyses suggested a cut-off score of 88/100 as optimum to distinguish patients from controls. This cut-off identified EOD with a sensitivity of 91.5% and a specificity of 96.4%. On considering individual subgroups, the lowest sensitivity was observed in bvFTD (83.3%), while values in the other dementia syndromes exceeded 90% (AD 96.8%, 90.9% for PPA and PCA).

Mean total ACE-III score and sub-scores on all domains were significantly higher in HC compared to EOD ( $p < 0.0001$  in all cases, details provided in Table-2). Post-hoc analyses revealed significant differences between HC and all four EOD subgroups in memory

( $p < 0.0001$ ), fluency ( $p < 0.0001$ ) and language ( $p \leq 0.023$ ). Significant differences in attention sub-scores were observed between HC and AD, PCA, PPA ( $p \leq 0.001$ ) but not bvFTD ( $p = 0.125$ ). Only AD and PCA had significantly lower mean visuospatial sub-scores compared to HC ( $p < 0.0001$  in both cases).

SMI was associated with significantly lower total ACE-III, fluency and memory sub-scores compared to HC ( $p \leq 0.014$ , see Table-2). However, ACE-III total score and all sub-scores were significantly higher in SMI compared to EOD ( $p \leq 0.002$  in all cases). A total ACE-III score of 88/100 distinguished EOD from SMI with high sensitivity (91.5%) and specificity (86.7%).

### **Within-EOD Group Differences**

Significant inter-group differences among the EOD subgroups were observed for mean attention ( $p = 0.014$ ), memory ( $p = 0.030$ ) and visuospatial ( $p < 0.0001$ ) sub-scores. On post-hoc analyses, AD was associated with significantly lower mean scores for attention ( $p = 0.017$ ) and memory ( $p = 0.026$ ) compared to bvFTD. PCA was associated with significantly lower mean visuospatial sub-scores compared to other three sub-groups ( $p < 0.0001$  in all cases).

Figure 2 illustrates the proportion of patients in each dementia subgroup with impaired performance (a score that is two standard deviations below the HC mean) in the different ACE-III domains. Significant within-EOD group differences in rates of impairment were observed in visuospatial skills ( $p = 0.004$ ) and in memory ( $p = 0.003$ ). The difference in rates of poor performance in visuo-spatial domain were driven by significantly higher rates in the PCA group compared to FTD and PPA ( $p \leq 0.0008$ ), while that in the memory domain was

driven by significant higher rates of memory impairment in AD compared to bvFTD ( $p=0.001$ ).

## DISCUSSION

This study based on a heterogeneous 'real life' EOD clinic population suggests the ACE-III is a reliable tool for screening for cognitive decline. The test takes approximately 15 minutes to undertake, differentiates EOD from healthy controls with high specificity and sensitivity, suggesting that it is an effective tool for screening for dementia.

The ACE-III also differentiated EOD patients from individuals with SMI. The younger age of individuals with SMI compared to EOD patients is most likely a reflection of the increasing risk of dementia with age. In addition, our definition of SMI included lack of progression on longitudinal follow up. A recent study investigating the predictors of cognitive decline in individuals with SMI reported that younger age was associated with reduced risk of developing cognitive decline on follow up.<sup>10</sup>

The lowest sensitivity was observed in bvFTD with 3/18 patients scoring above the cut-off for abnormal performance. This finding is consistent with current understanding that cognitive domains measured using the ACE-III can be intact in early stage bvFTD despite marked breakdown in behaviour.<sup>11</sup> This highlights the importance of formal evaluation of behaviour in suspected bvFTD. In addition, early cognitive changes in bvFTD often affects executive functioning, a heterogeneous domain which is difficult to evaluate comprehensively.<sup>12,13</sup> Executive function is represented in the ACE-III with a single task (verbal fluency), a limitation noted by its authors.<sup>4</sup> It is possible that additional impairment might be identified in bvFTD using more detailed examination of executive functions, or as suggested by some recent reports, using tasks of social cognitive skills.<sup>14,15</sup>



Whilst the ACE-III differentiated patients with dementia from HC with high sensitivity and specificity, there were few significant differences between dementia subgroups. Visuospatial performance in PCA was significantly worse than in other dementia syndromes, in line with the prominent visuo-perceptual deficits in these patients.

Patients with bvFTD displayed significant dysfunction in memory and language while performance on attention was similar to controls in line with previous findings.<sup>16</sup> Our observation of memory impairment in 60% of patients with bvFTD is also consistent with reports suggesting memory impairment is common in early-onset FTD.<sup>17</sup> However, both mean memory scores and rates of memory impairment were significantly worse in AD. Conversely, there were no significant differences between bvFTD and AD in performance on verbal fluency, a task where poor performance is classically associated with bvFTD. All dementia subgroups performed poorly on this task with no significant inter-group differences. The verbal fluency task is a complex task which places heavy demands on multiple fronto-striatal circuits, language production, and word retrieval functions. The integrity of these systems can be affected by pathology at multiple anatomical sites,<sup>13,18</sup> reducing the specificity of the task. In addition, the ACE-III is combines both letter and category fluency increasing the sensitivity of the task to a wide range of dementia syndromes.<sup>19,20</sup>

An unexpected finding was the lack of significant between-group differences in language performance. This contrasted with the ACE-III validation study where the only reported significant difference between dementia groups was in the language domain, with lower scores in PPA compared to bvFTD and AD.<sup>4</sup> Our results may be related to sample size or to differences in phenotypic expression in EOD. Non-amnesic variants have been reported more frequently in early-onset AD patients compared to late-onset disease.<sup>21</sup> It is conceivable

that subtle language impairment is more common in early-onset AD, and possibly bvFTD. The poor performance in the PCA group probably reflects the heavy reliance of the ACE-III language subtasks (e.g. object naming, reading) on intact visuospatial perception. Similarly, poor memory scores in PPA are likely to be at least partially influenced by the verbal nature of the memory sub-tasks in the ACE-III.

The main limitations of this study are its retrospective design, the use of a convenience sample of consecutive patients attending a tertiary memory clinic, and lack of pathological confirmation of final diagnoses. In addition, the study may be under-powered for small sized effects between diagnostic sub-groups. Further large scale, prospective studies would be ideal to confirm our findings.

Our findings, based on a heterogeneous clinic cohort, suggest that, notwithstanding its limitations, the ACE-III is a reliable tool for screening for cognitive decline in EOD. However, we would recommend that clinicians should use the ACE-III as a diagnostic adjunct and should consider, in the appropriate clinical context, the inclusion of a behavioural questionnaire and/or additional tasks of executive and language function.

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## COMPETING INTERESTS

The authors report no conflict of interests.

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## FIGURE LEGEND

**Figure 1.** This figure illustrates the rates of abnormal performance on the different ACE-III domains in healthy controls, individuals with subjective memory impairment, and patients with early onset dementia. **Key:** AD: Alzheimer's disease; bvFTD: behavioural variant frontotemporal dementia, PPA: primary progressive aphasia; PCA: Posterior cortical atrophy; HC: Healthy controls; SMI subjective memory impairment.



**Table 1** This table provides a summary of the basic characteristics of the EOD subgroups and those of controls. **Key** AD: Alzheimer’s disease; bvFTD: behavioural variant frontotemporal dementia, PPA: primary progressive aphasia; PCA: Posterior cortical atrophy; HC: Healthy controls; SMI subjective memory impairment; P1 refers to p value obtained on one-way ANOVA comparing healthy controls to patients with dementia; P2 refers to p value obtained on within group comparisons of the 4 dementia groups. P3 refers to p value obtained on comparing HC to individuals with subjective memory impairment.

	AD	n	bvFTD	n	PPA	n	PCA	n	SMI	n	HC	n	P1	P2	P3	
<b>Mean Age at Testing yrs (SD)</b>	<b>62.6 (5.3)</b>	31	<b>63.6 (4.9)</b>	18	<b>62.2 (5.4)</b>	11	<b>61.1 (5.3)</b>	11	<b>54.0 (6.3)</b>	15	66.6 (8.6)	28	0.065	0.643	<0.000	
<b>Males %</b>	<b>48.4%</b>	31	<b>44.4%</b>	18	<b>72.7%</b>	11	<b>18.2%</b>	11	<b>60.0%</b>	15	<b>57.1%</b>	28	0.110	0.083	0.977	
<b>Median Disease duration (yrs)</b>	<b>2.0</b>	31	<b>4.0</b>	17	<b>4.0</b>	11	<b>4.0</b>	11	-	-				0.243	0.243	
<b>Education</b>																
<b>&lt; 16 years</b>	<b>46.7%</b>	30	<b>27.8%</b>	18	<b>27.3%</b>	11	<b>36.4%</b>	11	<b>26.7%</b>	15	<b>53.6%</b>	28				
<b>16-18 years</b>	<b>26.7%</b>		<b>44.4%</b>		<b>72.7%</b>		<b>45.5%</b>		<b>46.7%</b>		<b>42.9%</b>		0.179	0.362	0.059	
<b>&gt;18 years</b>	<b>16.7%</b>		<b>27.8%</b>		<b>0.0%</b>		<b>18.2%</b>		<b>26.7%</b>		<b>3.6%</b>					

**Table 2** This table provides a summary of the mean scores of the EOD subgroups and those of controls. Standard deviations are shown in parenthesis. **Key** AD: Alzheimer's disease; bvFTD: behavioural variant frontotemporal dementia, PPA: primary progressive aphasia; PCA: Posterior cortical atrophy; HC: Healthy controls; SMI subjective memory impairment; P1 refers to p value obtained on one-way ANOVA comparing healthy controls to patients with dementia; P2 refers to p value obtained on within group comparisons of the four dementia groups. P3 refers to p value obtained on comparing HC to individuals with subjective memory impairment.

	AD	bvFTD	PPA	PCA	SMI	HC	P1	P2	P3
<b>Total ACEIII (max100)</b>	61.0 (17.0)	72.5(3.1)	61.3(23.7)	59.6 (15.4)	92.3 (3.7)	96.7(3.4)	<0.0001	0.104	0.001
<b>Attention (max18)</b>	11.9 (4.2)	15.4 (2.4)	13.4 (5.0)	11.7 (2.6)	17.5 (0.6)	17.8(0.5)	<0.0001	0.014	0.107
<b>Memory (max24)</b>	11.5 (5.0)	16.1 (6.7)	11.1 (6.1)	14.7 (6.1)	23.3 (1.8)	24.8(2.2)	<0.0001	0.030	0.003
<b>Fluency (max14)</b>	5.8 (3.2)	5.2 (3.0)	5.5 (4.1)	6.8 (3.8)	11.4 (2.0)	13.0(1.3)	<0.0001	0.676	0.014
<b>Language (max26)</b>	20.5 (4.0)	21.1 (5.8)	18.7 (7.0)	21.1 (2.3)	25.5 (0.7)	25.7(0.7)	<0.0001	0.599	0.168
<b>Visuo-spatial skills (max16)</b>	11.3 (4.1)	13.6 (2.8)	13.0 (3.4)	4.9 (3.0)	15.6 (0.7)	15.5(0.8)	<0.0001	<0.0001	0.820

