Validation of Addenbrooke's Cognitive Examination-Revised for the Differential Diagnostics of Frontotemporal Dementia and Alzheimer's Disease in Lithuanian-Speaking Population

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Summary. *Background*: Addenbrooke's Cognitive Examination – Revised (ACE-R) is a cognitive screening test, reportedly sensitive for many types of dementia, including Alzheimer's Disease (AD) and frontotemporal Dementia (FTD). Studies investigating the specificity of ACE-R have not yielded a unanimous solution that would allow clinicians to make a more accurate differential diagnosis of AD and FTD. In this study we aimed to validate the Lithuanian version of ACE-R (ACE-R^{LT}) as a test, which can differentiate AD from FTD in Lithuanian-speaking population.

Methods: ACE-R^{LT} is a 100-score test battery that allows to assess six cognitive domains. A total of 115 patients with dementia (30 with mild-moderate FTD, and 85 mild-moderate AD) and 95 healthy age, gender and education matched controls were included in the study.

Results: Patients with AD can be differentiated from FTD by lower scores on orientation, attention and, memory, while patients with FTD can be differentiated from AD by lower scores on verbal fluency, language, and naming. It was found that VLOM ratio was able to differentiate AD from FTD. The sensitivity for diagnosing AD of VLOM ratio >3.2 was 64.7% with specificity of 90.2%, while the sensitivity for diagnosing FTD of VLOM ratio <2.2 was 76.7% with specificity of 67.1%.

Conclusions: The results of this study provide objective validation of the ACE-R^{LT} as a tool for differential diagnostics of FTD and AD in Lithuanian-speaking population.

Keywords: Addenbrooke's Cognitive Examination – revised, Alzheimer's disease, frontotemporal dementia, differential diagnostics.

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INTRODUCTION

Adequate care of dementia patients requires recognizing them as having a dementia syndrome, and evaluating for the specific cause of the dementia. The European Federation of Neurological Societies (EFNS) recommends that a neuropsychological evaluation be done on all patients with suspected dementia as part of the comprehensive neurodiagnostic evaluation, which consists of well-standardized tests of cognition [1]. Despite this, more comprehensive cognitive batteries such as the cognitive section (CAMCOG) of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) and the Dementia Rating Scale (DRS) are beyond the routine evaluation of the primary care setting, as their administration requires specialized test equipment or trained personnel [2, 3].

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Therefore, there is a need for short and easily accessible and administered dementia screening tools.

The possibility of disease-modifying treatments for AD is making it vital to establish an early and accurate diagnosis, preferably in the predementia stage of the disease [4]. The reflection of the past two decades is that a substantial number of patients previously diagnosed with AD have other pathologies, notably frontotemporal dementia and Lewy bodies dementia [5, 6]. Therefore, new dementia screening tests that can differentiate various types of dementia, are needed.

The Addenbrooke's Cognitive Examination – Revised (ACE-R) is a brief cognitive dementia screening test battery recently adapted to Lithuanian population, which could be recommended as the most appropriate tool for dementia screening [7, 8]. The ACE-R is a brief, 15–20-minute test battery originally designed to detect and classify different kinds of dementia, particularly AD and frontotemporal dementia, without the use of specialized test equipment [7]. The maximum score is 100, weighed as follows: orientation (10), attention (8), memory (26), verbal fluency (14), language (26), and visuospatial ability (16).

The Lithuanian version of ACE-R was validated on 42 patients (37 patients with dementia and 5 patients with mild cognitive impairment) and 58 controls [8]. When the lower cut-off score of 74 was used, the sensitivity of the ACE-R^{LT} to detect dementia was 91%. When the lower cut-off score of 77 was used, the sensitivity of the ACE-R^{LT} to detect mild cognitive impairment was 87.7%. Compared to MMSE the rate of dementia and mild cognitive impairment detection was higher. In conclusion, the ACE-R^{LT} was found to be a sensitive and reliable tool to detect cognitive decline due to dementia or mild cognitive impairment.

In 2006 the team led by Eneida Mioshi and John Hodges that developed the ACE-R, investigated its ability to differentiate between differentiating subtypes of dementia including AD and FTD. They argued that differential diagnosis of AD and FTD can be done by using a subscore, the VLOM ratio (VLOM ratio = [verbal fluency + language] ÷ [orientation + delayed recall]) [9], specifically the VLOM ratio >3.2 for the diagnosis of AD, and the VLOM ratio <2.2 for the diagnosis of FTD is questioned. But other authors have questioned the utility of VLOM ratio in identifying FTD [10]. It has been reported that the diagnostic utility of the VLOM ratio <2.2 for the diagnosis of FTD showed poor sensitivity but good specificity, with accordingly very poor and excellent positive and negative utility indexes, respectively. Further research is needed to establish the use of the ACE-R for differential diagnosis of AD and FTD.

OBJECTIVE

Our study sought to investigate the ability of the ACE-R to accurately differentiate mild-moderate Alzheimer's disease from mild-moderate frontotemporal dementia.

METHODS

Participants

We recruited the following participants: 85 patients with early mild-moderate AD, 30 patients with mild-moderate FTD, and 94 healthy controls. Consecutive referrals to the Neurology Department of the Vilnius University Hospital Santariskiu Clinics were screened for possible inclusion into the study. The inclusion for all the groups are displayed in Table 1. Participants were excluded from the study, if they had a concurrent degenerative CNS disease (for example, Parkinson's disease) or other primary nervous system diseases (for example, epilepsy), an acute

Table 1. **Inclusion criteria for the participant recruitment**

	AD group	FTD group	Control group
Patients fulfilled National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD at the time of testing [11].	+		
Patients were diagnosed with mild-moderate Alzheimer's disease (had scores 18 points on the Mini-Mental State Examination [12])	+	+	
Patients were 50 years old or older at the time of recruitment	+	+	+
Patients' education was at least 4 years.	+	+	+
Patients had sufficient vision and hearing to complete the ACE-R.	+	+	+
Patients fulfilled consensus criteria for frontotempolar dementia [13]. In keeping with previous studies [14–16], the term frontotempolar dementia was used as a general label for all focal lobar degenerations, which include patients with core features of personality and behavioural changes (frontal variant FTD), nonfluent spontaneous speech (progressive nonfluent aphasia), and fluent empty spontaneous speech with semantic breakdown (semantic dementia).		+	
Patients were diagnosed with mild-moderate frontotempolar dementia (had scores 18 points on the Mini-Mental State Examination [12]).		+	
Participants had scores 27 points on the Mini-Mental State Examination [12].			+

stroke, primary psychiatric disorder (for example, schizophrenia), clinically significant kidney or liver disease, thyroid dysfunction or vitamin B12 deficiency. All participants were between 50 and 88 years old at the time of recruitment and were well matched for age, sex, and education. Spouses or friends of the participating patients were recruited as healthy controls. All participants had sufficient knowledge of Lithuanian language to participate in the study. All study participants were able to perform all of the tasks in the test. Participants who had visual problems were asked to wear glasses. None of the participants had severe hearing or other sensory impairments. The study was approved by the Lithuanian Bioethics Committee.

Instrument

Lithuanian version of Addenbrooke's Cognitive Examination-Revised (ACE-R). The ACE-R^{LT} takes between 12 and 20 min (average 16) to administer and score in a clinical setting. It contains 5 sub-scores, each one representing one cognitive domain: attention/orientation (18 points), memory (26 points), fluency (14 points), language (26 points) and visuospatial (16 points). ACE-R^{LT} maximum score is 100, composed by the addition of the all domains.

RESULTS

Demographics. Demographic characteristics of the patient and control groups are summarized in Table 2. The groups were matched on age (one-way ANOVA, F[2, 206]=1.66; p=0.193), years of education (one-way ANOVA, F[2, 206]=0.501; p=0.607) and gender (^{2}, p=0.883). To evaluate whether the demographic variables had an effect on performance on the ACE-R test scores, we formed general linear regression models for the patient and control groups. In Alzheimer's disease group neither age (F=1.288; Beta=-0.178; p=0.110), nor gender (F=7.588; Beta=-0.034; p=0.759) or education (F=3.366; Beta=0.149; p=0.182) had an effect on ACE-R scores. In frontotempolar disease group only education (F=5.121; Beta=0.239; p<0.001) had an effect on ACE-R. In control group both age (F=2.174; Beta=-0.387; p<0.001) and education (F=2.869; Beta=0.454; p<0.001) had an effect, while gender did not (F=0.101; Beta=0.025; p=0.769).

Validity and reliability of the ACE-R^{LT}. Two methods were used to calculate the validity of ACE-R^{LT}. We carried out a logistic-regression analysis to evaluate the ACE-R^{LT} ability to correctly classify people with or without dementia. The logistic-regression was carried out with two target variables: patients with dementia group (AD and FTD group) versus no-dementia group (healthy controls). The total ACE-R score correctly classified 94.3% of the cases. We also carried ROC analysis to evaluate ACE-R^{LT} ability to discriminate the dementia group. The trade-off between sensitivity (true positive rate) and 1–specificity (false positive rate) of the ACE-R in diagnosing AD in a patient population with and without a later confirmed AD is shown in the ROC curve in Figure. The area under the ROC curve is 0.994, which suggests that the ACE-R has a high specificity for a large range of sensitivities. At 74, the previously recommended cut-off score for clinical use in the detection of dementia, the ACE-R showed a sensitivity of 100%, and a specificity of 91.5% for Alzheimer disease in our study. Patients with dementia tend to fail the ACE-R (score below the recommended cut-off of 74 points) significantly more often than controls (chi square; p<0.001). 100% percent of patients with dementia fell below the cut-off of 74 points for dementia. Also, only 8.5% of healthy controls fell below the cut-off for dementia. Reliability of the ACE-R^{LT} was measured in terms of internal consistency, using Cronbach's alpha coefficient. The Cronbach's alpha for the ACE-R^{LT} was 0.904 (0.8 is considered excellent).

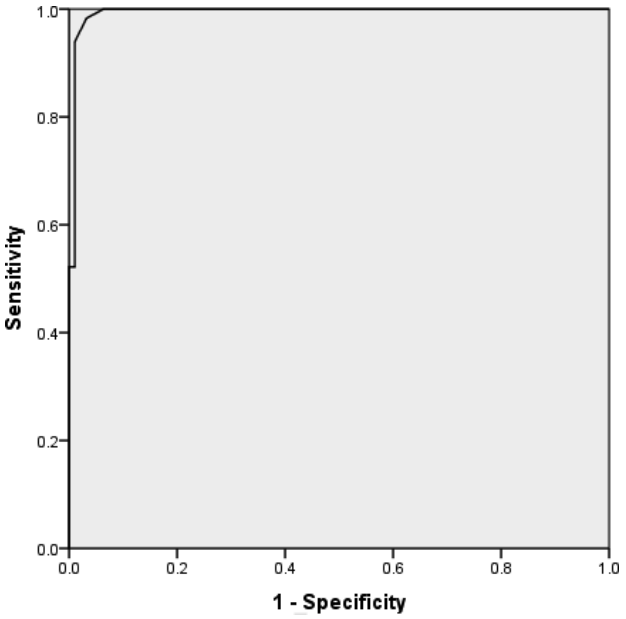

Figure. **Receiver Operating Characteristics (ROC) of the Addenbrooke's Cognitive Examination-Revised (ACE-R) as a Test for Dementia.**

Table 2. **Demographic Characteristics of the Patient and Control Groups.**

	Total	AD	FTD	Controls
% females	63.2%	63.5%	66.7%	67.0%
Mean age in years (SD)	66.42 (±9.1)	66.33 (±7.92)	65.03 (±8.47)	66.93 (±10.26)
Years of Education (SD)	11.48 (±3.28)	11.15 (±3.41)	11.00 (±4.03)	11.93 (±2.86)

Note. SD: Standard deviation

Differentiating AD and FTD. Mann-Whitney U-test was used to compare ACE-R^{LT} performance of AD and FTD groups. A series of Mann-Whitney U-tests revealed significant mean differences (Table 3) between the groups for orientation, attention, memory, letter fluency, language, and naming scores. The AD group showed significant deficits in orientation, attention, name and address learning, name and address delayed recall and memory compared to FTD group. The FTD group showed significant deficits in letter fluency, language, and language to AD group. In order to translate this pattern of scoring into an index useful in differentiating AD and FTD subgroups, we calculated the ratio of scores on verbal fluency plus language to orientation plus name and address delayed recall memory. This VLOM ratio tended to be higher in patients with AD and lower in those with FTD. The sensitivity for diagnosing AD of VLOM ratio >3.2 was 64.7% with specificity of 90.2%. 64.7% of patients with AD had a VLOM ratio of >3.2. The sensitivity for diagnosing FTD of VLOM ratio <2.2 was 76.7% with specificity of 67.1%. 63.3% of patients with FTD had a VLOM ratio of <2.2.

Table 3. **Comparison of mean scores of AD group and FTD group on components of ACE-R^{LT}**

	AD	FTD	p Value
Orientation	6.56	8.9	<0.001
Attention	5.24	7.27	<0.001
Memory	8.26	16.83	<0.001
Name and address learning	3.53	5.7	<0.001
Name and address delayed recall	0.55	3.47	<0.001
Verbal Fluency	6.07	5.4	0.086
Letter Fluency	3.49	2.67	0.002
Category Fluency	2.58	2.84	0.647
Language	17.21	10.67	<0.001
Naming	6.8	2.87	<0.001
Visuospatial	11.4	12.4	0.105

DISCUSSION

Research with the ACE-R^{LT} suggests that it is a reliable test for the early detection of dementia and meets the standards required by such an instrument [17]. Our study has shown that the ACE-R^{LT} could be used to a limited extent in differential diagnostics of AD and FTD.

The demographic differences had no effect on the study results, because the Alzheimer's disease, frontotempolar dementia, and control groups did not differ significantly by age, gender or education. In our study, age had a significant influence on ACE-R^{LT} performance (in line with previous findings by Margeviciute et al. (2013)), which again emphasizes the need for age-specific ACE-R norms. Having the importance of age on overall performance in mind, it appears to be worthwhile to consider establishing different ACE-R^{LT} cut-off points for the young-old and the old-old groups later on in the result analysis, as had been done in the Pigliautille and colleagues' (2011) adaptation of ACE-R. Future research in this field is needed to test this hypothesis.

Consistent with the original observations by Margeviciute et al. (2013) we found that ACE-R^{LT} is reliable and valid test for dementia screening. The reliability of the ACE-R^{LT} is evident in its high internal consistency, which indicates that all its component scores contribute to the measurement of cognitive functions and correlate well with the composite score, which in turn determines the presence or absence of dementia. The validity of the ACE-R^{LT} as dementia screening tool is evident in its ability to identify people with dementia with high sensitivity and specificity. The sensitivity of ACE-R^{LT} is better than reported by Margeviciute et al. (2013). This could be due to the exclusion of vascular dementia in our study.

The ACE-R^{LT} could be used in AD and FTD differential diagnostics. Patients with AD can be differentiated from FTD by lower scores on orientation, attention and memory. Meanwhile, patients with FTD can be differentiated from AD by lower scores on letter fluency, language, and naming. Concerning the diagnosis of AD, we found that a VLOM ratio >3.2 had analogous sensitivity and specificity to detect AD with Mathuranath et al. (2000) results. The majority of patients with AD (64.7%) had a VLOM ratio >3.2. Also, concerning the diagnosis of FTD, we found analogous sensitivity and specificity to detect FTD with Mathuranath et al. (2000) results. The majority of patients with FTD (63.3%) had a VLOM ratio <2.2. The VLOM ratio is a ratio between scores in language tasks and memory tasks: a lower score indicates specific deficit in language versus memory functions. We argue that the disparities found by Mathuranath et al. (2000) and Bier et al. (2004) could be explained by differences of dementia groups in those studies. In Mathuranath et al. (2000) study dementia group consisted of patients with primary progressive aphasia, semantic dementia or the pure frontal form of frontotempolar dementia. Meanwhile, Bier et al. (2004) dementia group had no case of primary progressive aphasia or semantic dementia among the FTD patients, who all presented with the pure frontal form of the disease. We think that a low (<2.2) VLOM ratio may be effective in diagnosing the form of FTD with selective language deficit, which is rarely obtained in the pure frontal form of the disease.

We conclude that the ACE-R^{LT} is a very accurate test for the detection of dementia and should be used in the everyday clinical practice and is fairly effective in differential diagnostics of AD and FTD. The contradictory results of our and previous studies show that the VLOM ratio may be less effective in discriminating the frontal variant of FTD when used as originally proposed. Re-defining the VLOM ratio or its cut-off could be a way to increase its sensitivity. Further prospective studies are needed to evaluate possible modifications for various variants of FTD and their efficiencies.

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TAISYTO ADENBRUKO KOGNITYVINIO TYRIMO VALIDIZACIJA FRONTOTEMPORALINĖS DEMENCIJOS IR ALZHEIMERIO LIGOS DIFERENCINEI DIAGNOSTIKAI LIETUVIŠKAI KALBANČIOJE POPULIACIJOJE

Santrauka

Taisytas Adenbruko kognityvinis tyrimas yra validus kognityvinis patikros testas, galimai jautrus įvairių formų demencijoms, tarp jų Alzheimerio ligai (AD) ir frontotemporalinei demencijai (FTD). Tyrimai, kurių metu buvo tirtas ACE-R specifiškumas, nedavė vienareikšmio atsakymo, kaip testas gali padėti klinicistam tikslinti Alzheimerio ligos ar frontotemporalinės demencijos diferencinę diagnozę. Šiame tyrime mes išsikėlėme tikslą validizuoti lietuviškąją ACE-R versiją (ACE-R (LT)) kaip testą, kuris gali diferencijuoti AD nuo FTD lietuviškai kalbančioje populiacijoje.

Metodai: ACE-R (LT) yra 100 balų testas, kuris padeda įvertinti šešias kognityvines sritis. 115 pacientų su demencija (30 su lengva-vidutine FTD ir 85 su lengva-vidutine AD) ir 95 sveiki suporuoti pagal amžių, lytį ir išsilavinimą kontrolinės imties tiriamieji buvo įtraukti į tyrimą.

Rezultatai: Pacientai su AD gali būti atskirti nuo FTD, remiantis prastesniais orientacijos, dėmesio ir atminties rezultatais, tuo tarpu pacientai su FTD gali būti atskirti, remiantis prastesniais žodinio sklandumo, kalbos ir įvardijimo rezultatais. Buvo rasta, kad VLOM koeficientas gali diferencijuoti AD nuo FTD. VLOM koeficiento > 3,2 jautrumas yra 64,7 %, o specifiškumas – 90,2 %, diagnozuojant AD, o VLOM koeficiento < 2,2 jautrumas yra 76,7 %, o specifiškumas – 67,1 %, diagnozuojant FTD.

Išvados: Tyrimo rezultatai patvirtina, kad ACE-R (LT) yra tinkamas instrumentas, kurį galima taikyti FTD ir AD diferencinėje diagnostikoje lietuviškai kalbančioje populiacijoje.

Raktažodžiai: taisytas Adenbruko kognityvinis tyrimas, Alzheimerio liga, frototemporalinė demencija, diferencinė diagnostika.