Validation of Addenbrooke's Cognitive Examination-Revised for the Differential Diagnostics of Dementia with Lewy Bodies and Alzheimer's Disease in Lithuanian-speaking Population

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Summary. *Background.* Currently, it is recognised that movement disorders, such as Parkinson's and related diseases, also have a cognitive component and those diseases can even progress in some patients to dementia. Therefore, a cognitive assessment is useful in evaluating movement disorders. There is a need for having more clinical tools for differential diagnostics between DLB and AD. The Addenbrooke's Cognitive Examination-Revised can meet this need as it is a brief sensitive dementia screening test. The Lithuanian version of ACE-R (ACE-R^{LT}) was shown to be able to detect dementia, but further research is still lacking in establishing the use of the ACE-R for differential diagnostics of AD and DLB. Accordingly, the aim of this study was to investigate the ability of the ACE-R to accurately differentiate mild-moderate Alzheimer's disease from mild-moderate dementia with Lewy bodies.

Participants and methods. Seventy three patients with early mild-moderate AD and 30 patients with mild-moderate DLB were evaluated with the ACE-R, the test which consists of the following domains: orientation, attention, memory, verbal fluency, language and visuospatial ability, with maximum total score 100. The results were compared with those obtained in 86 healthy controls. The one-way ANOVA, logistic-regression analysis, ROC analysis and Mann-Whitney U-test were done for statistical analysis.

Results. In AD group neither age ($p=0.060$), nor gender ($p=0.466$) or education ($p=0.206$) had an effect on ACE-R scores. In DLB group neither age ($p=0.249$) nor gender ($p=0.615$) or education ($p=0.360$) had an effect on ACE-R scores. In control group both age ($p<0.001$) and education ($p<0.001$) had an effect, while gender did not ($p=0.438$). At 74, the previously recommended cut-off score for clinical use in the detection of dementia, the ACE-R^{LT} showed a sensitivity of 100%, and a specificity of 90.5% for AD in our study. The Cronbach's alpha for the ACE-R^{LT} was 0.912. AD group was significantly more likely to score below the recommended cut-off scores for memory and language subtests than the DLB group (chi-square; $p<0.0001$). The DLB group was significantly more likely to score below the recommended cut-off scores for verbal fluency and visuospatial abilities subtests than the AD group (chi square; $p<0.0001$).

Conclusions. The ACE-R^{LT} appears to be a reliable and valid tool for differential diagnostics of DLB and AD in Lithuanian speaking population. The cognitive assessment using ACE-R^{LT} indicated that in DLB verbal fluency and visuospatial abilities were more impaired compared to AD. And in AD memory and language performance were worse than in DLB.

Keywords: Alzheimer's disease, Dementia with Lewy bodies, Addenbrooke's Cognitive Examination, neurodegenerative diseases, movement disorders, cognitive symptoms, neuropsychological assessment.

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Abrevations:

ACE-R – Addenbrooke's Cognitive Examination-Revised
AD – Alzheimer's disease,
DLB – disease with Lewy bodies,
PD – Parkinson's disease.

INTRODUCTION

Nowadays it is well accepted that Parkinson's disease (PD) should be considered more than just a motor disorder, which is why cognitive impairments that sometimes tend to progress to dementia should not be forgotten [1]. Although this was not reflected in the staging scale for PD developed by Hoehn and Yahr (1967), which referred to motor symptoms only, the broader Unified Parkinson's Disease Rating Scale (UPDRS) does encompass intellectual function. Histological features of PD lay emphasis on the existence of Lewy bodies, intracytoplasmic rounded eosinophilic inclusions in brainstem monoaminergic and cholinergic neurons. Patients with dementia and parkinsonism, often with concurrent Alzheimer's disease (AD) type pathology, and typical histological findings in the neocortex were reclassified to a syndrome under a name of dementia with Lewy bodies (DLB) [1].

Clinical and pathological diagnostic criteria for DLB have been developed and validated [3]. Clinical features such as progressive cognitive decline with prominent deficits in attention, visuospatial abilities, and executive function, along with an amount of other fundamental features which are essential for the assessment of the diagnosis of probable (two features) or possible (one feature) DLB, namely fluctuating cognition with pronounced variations in attention (the 'unstable platform of attention'), recurrent visual hallucinations, and spontaneous motor features of parkinsonism, are by long odds considered pivotal for DLB. Other features such as marked neuroleptic sensitivity and syncopal episodes also favour the diagnosis of DLB [4].

It has been realized in the past two decades that a vital number of people who were considered to suffer from AD should be reconsidered having other pathologies, notably DLB [5, 6]. There is a possibility of development of disease-modifying treatments for AD in the near future. Therefore, it is crucial to differentiate AD from other forms of dementia and to establish an early and accurate diagnosis, preferably in the pre-dementia stage [7]. 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 and differential diagnosis [8, 9]. The ACE-R is a brief, 15–20-minute test battery aiming at the detection and classification of different forms of dementia without the use of specialized test equipment [8]. The maximum score is 100, weighed as follows: orientation (10), attention (8), memory (26), verbal fluency (14), language (26), and visuospatial ability (16). In 2005 the team led by Thomas Bak has found the ACE-R is able to distinguish between atypical parkinsonian disorders and Alzheimer's disease. It has been established that the Lithuanian version of ACE-R (ACE-R^LT) is able to detect dementia. Nevertheless, no further research using ACE-R^LT, which could help differentiate AD from DLB,

was carried out [9]. Further research is needed to establish the use of the ACE-R for differential diagnosis of AD and DLB.

OBJECTIVE

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

METHODS

Participants

We recruited the following participants: 73 patients with early mild-moderate AD, 30 patients with mild-moderate DLB, and 86 healthy controls. Consecutive referrals to the Neurology Department of the Vilnius University Hospital Santariskiu Clinics were screened for possible inclusion into the study. Participants were excluded from the study, if they had a concurrent degenerative central nervuos system disease (for example, Parkinson's disease) or other primary nervous system diseases (for example, epilepsy), an acute 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, had at least 4 years of education and were well matched for age, sex, and education. All patients in the AD group 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 in the AD group were diagnosed with mild-moderate Alzheimer's disease (had scores 18 points on the Mini-Mental State Examination [12]). All patients in the DLB group fullfilled Consortium on Dementia with Lewy bodies established criteria for probable DLB at the time of testing [13]. Spouses or friends of the participating patients were recruited as healthy controls, who had scores 27 points on the Mini-Mental State Examination [12]. 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^LT). 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

Table 1. **Demographic Characteristics of the Patient and Control Groups**

	Total	AD	DLB	Controls
% females	64.9%	63.5%	60.0%	64.6%
Mean age in years (SD)	66.03 (±8.67)	65.58 (±7.21)	63.63 (±7.11)	67.24 (±10.07)
Years of Education (SD)	11.93 (±2.81)	11.83 (±3.11)	11.73 (±2.75)	12.07 (±2.58)

Note. SD: Standard deviation

(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 1. The groups were matched on age (one-way ANOVA, F[2, 186]=2.09; p=0.126), years of education (one-way ANOVA, F[2, 186]=0.219; p=0.804) and gender (x^2, p=0.643). 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=2.092; Beta=-0.241; p=0.060) nor gender (F=0.734; Beta=0.084; p=0.466) or education (F=1.278; Beta=0.147; p=0.206) had an effect on ACE-R scores. In dementia with Lewy bodies disease group neither age (F=1.179; Beta=-0.222; p=0.249) nor gender (F=0.509; Beta=-0.096; p=0.615) or education (F=0.931; Beta=-0,176; p=0.360) had an effect on ACE-R scores. In control group both age (F=0.174; Beta=-0,355; p<0.001) and education (F=3.997; Beta=0.385; p<0.001) had an ef-

fect, while gender did not (F=0.779; Beta=0.075; p=0.438).

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 DLB group) versus no-dementia group (healthy controls). The total ACE-R^{LT} score correctly classified 99.5% 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^{LT} in diagnosing dementia in a population with and without a later confirmed dementia is shown in the ROC curve in Figure. The area under the ROC curve is 0.992, which suggests that the ACE-R^{LT} 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^{LT} showed a sensitivity of 100% and a specificity of 90.5% for Alzheimer disease in our study. Patients with dementia tend to fail the ACE-R^{LT} (score below the recommended cut-off of 74 points) significantly more often than controls (chi square; p<0.001). 100% of patients with dementia fell below the cut-off of 74 points for dementia. Also, only 5.8% 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 0.912 (0.8 is considered excellent).

Differentiating AD and DLB. Mann-Whitney U-test was used to compare ACE-R^{LT} performance of AD and DLB groups. A series of Mann-Whitney U-tests revealed significant mean differences (Table 2) between the groups memory, verbal fluency, language and visuospatial scores. The AD group showed significant deficits in memory and
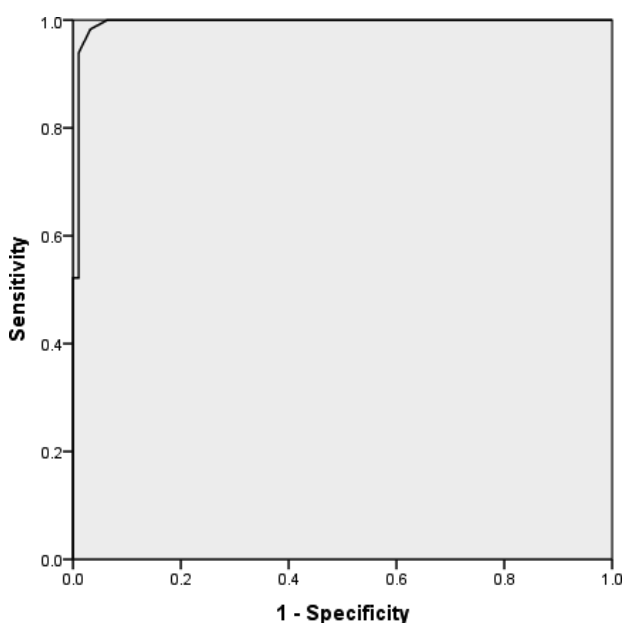

Fig. **Receiver Operating Characteristics (ROC) of the ACE-R^{LT} as a Test for Dementia**

Table 2. **Comparison of mean scores of AD group and DLB group on components of ACE-R^{LT} (in parenthesis SD)**

	AD	DLB	p value
Orientation	6.548 (±2.06)	6.767 (±1.28)	0.95
Attention	5.247 (±1.26)	5.367 (±1.36)	0.572
Memory	7.973 (±3.18)	12.833 (±2.15)	<0.001
Verbal Fluency	4,904 (±2.59)	3,3 (±1.18)	<0.001
Language	17,548 (±3.95)	22,2 (±1.94)	<0.001
Visuospatial	11,548 (±2.56)	7,5 (±1.85)	<0.001

Table 3. Proportion (in percent) of Subjects Scoring Below the Recommended Cut-off Score for Dementia on the ACE-R^{LT} (in parenthesis SD)

	Mild-moderate Alzheimer's disease	Mild-moderate Dementia with Lewy bodies	^{2} value
Attention and orientation	98.6%	93.3%	0.203
Memory	97.2%	60.0%	<0.001
Verbal fluency	79.5%	96,7%	<0.001
Language	78.4%	23.4%	<0.001
Visuospatial abilities	42.5%	100%	<0.001

language compared to DLB group. The proportions of AD and DLB groups scoring below the recommended cut-off scores for dementia on ACE-R are shown in Table 3. Alzheimer's disease group was significantly more likely to score below the recommended cut-off scores for memory and language subtests than the DLB group (chi-square; p<0.0001). The DLB group was significantly more likely to score below the recommended cut-off scores for verbal fluency and visuospatial abilities subtests than the AD group (chi square; p<0.0001).

DISCUSSION

Previous research suggests that the ACE-R^{LT} is a reliable test for the early detection of dementia and meets the standards required for such an instrument [14]. Our study has shown that the ACE-R^{LT} could be used in differential diagnostics of AD and DLB.

The demographic differences had no effect on the study results, because the AD, DLB, 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 DLB differential diagnostics. Patients with AD can be differentiated

from DLB by lower scores on memory. Memory is impaired both in AD and DLB, but memory impairments are greater in AD. Language is relatively preserved in DLB. Meanwhile, patients with DLB can be differentiated from AD by lower scores on verbal fluency and visuospatial abilities. Verbal fluency is impaired both in AD and DLB, but verbal fluency impairments are greater in DLB. Visuospatial abilities are relatively better preserved in AD.

We conclude that the ACE-R^{LT} is an accurate test for the detection of dementia and could be used in the everyday clinical practice and is fairly effective in differential diagnostics of AD and DLB. Further prospective studies are needed to evaluate the possible use of ACE-R^{LT} in differential diagnostics of AD and other parkinsonian syndromes.

CONCLUSIONS

1. In both DLB and AD groups, demographic characteristics (age, education, gender) did not have an effect on cognitive performance in ACE-R test.
2. In a group of healthy controls, age and education had an effect on cognitive performance in the ACE-R test, but gender did not.
3. The ACE-R was proved to be a reliable and valid tool in detecting dementia in Lithuanian-speaking population.
4. The ACE-R could differentiate between mild-moderate AD and mild-moderate DLB in Lithuanian-speaking population.
5. The distinct patterns of cognitive impairments in DLB compared to AD were found. Memory and language impairments were greater in AD, while verbal fluency and visuospatial abilities were more affected in DLB.

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ADENBRUKO KOGNITYVINIO TYRIMO TAISYTOS METODIKOS VALIDIZACIJA DIFERENCINEI LEVI KŪNELIŲ IR ALZHEIMERIO LIGŲ DIAGNOSTIKAI LIETUVIŠKAI KALBANČIOJE POPULIACIJOJE

Santrauka

Įvadas. Šiuo metu pripažįstama, kad vertinant judėjimo sutrikimus svarbu atsižvelgti ir į kognityvinius procesus. Progresuojant šioms ligoms, kai kuriems pacientams išsivysto demencija. Todėl tikslinga ieškoti daugiau priemonių Alzheimerio ligos ir Levi kūnelių demencijos diferencinei diagnostikai. Tokia priemone gali būti Adenbruko kognityvinio tyrimo taisyta metodika (angl. *Addenbrookes's Cognitive Examination-Revised*, ACE-R). Originalus testas bei jo lietuviška versija (ACE-R^{LT}) pasižymi kompaktiškumu ir jautrumu aptinkant demenciją.

Šio tyrimo tikslas yra patikrinti, kaip ACE-R^{LT} diferencijuoja Alzheimerio ir Levi kūnelių ligas.

Tiriamieji ir tyrimo metodai. Tyrime dalyvavo 73 pacientai, kuriems diagnozuota lengva–vidutinio sunkumo Alzheimerio liga, 30 pacientų, kuriems diagnozuota lengva–vidutinio sunkumo Levi kūnelių liga, ir 86 kontrolinės grupės tiriamieji, neturintys diagnozuotų neurologinių ar psichikos sutrikimų. Su kiekvienu iš tiriamųjų buvo atliktas ACE-R testas, apimantis orientacijos, dėmesio, atminties, žodinio sklandumo ir erdvinių gebėjimų įvertinimą. Maksimalus įvertinimas yra 100 balų. Statistinei analizei naudota vienfaktorinė dispersinė analizė ANOVA, logistinės regresijos analizė, ROC kreivių analizė ir Mano-Vitnio U kriterijus.

Rezultatai. Alzheimerio ligos grupėje nei tiriamųjų amžiaus (p = 0,060), nei lyties (p = 0,466), nei išsilavinimo (p = 0,206) poveikis ACE-R rezultatams nebuvo pastebėtas. Levi kūnelių grupėje nei tiriamųjų amžiaus (p = 0,249), nei lyties (p = 0,206), nei išsilavinimo (p = 0,615) poveikis ACE-R rezultatams nebuvo pastebėtas. Kontrolinėje grupėje pastebėtas ir amžiaus (p < 0,001), ir išsilavinimo (p < 0,001) poveikis ACE-R rezultatams, bet lyties sąsajos su rezultatais nebuvo nustatytos (p = 0,438). Šiame tyrime ACE-R^{LT} pasižymėjo itin aukštu patikimumu (Kronbacho = 0,912).

Ribiniu normos įverčiu buvo pasirinkti Alzheimerio ligai aptikti ankstesnių tyrėjų pasiūlyti 74 balai. Šiame tyrime nustatytas ACE-R^{LT} 100 % jautrumas ir 90,5 % specifiškumas. AD grupės balai atminties ir kalbos subskalėse statistiškai reikšmingai mažesni negu ribinis normos įvertis ir DLB grupės balai (chi-kvadrato kriterijus, p < 0,0001). DLB grupė surinko statistiškai reikšmingai mažiau balų negu rekomenduojamas ribinis normos įvertis, palyginus su AD, žodinio sklandumo erdvinių gebėjimų subskalėse (chi-kvadratas, p < 0,0001).

Išvados. Tyrimu atskleista, kad ACE-R^{LT} yra patikima ir validi priemonė diferencinei DLB ir AD diagnostikai lietuviškai kalbančioje populiacijoje. Taikant ACE-R^{LT}, nustatyta, kad Levi kūnelių demencija sergantys pacientai prasčiausiai atliko žodinio sklandumo ir erdvinių gebėjimų užduotis, sergantieji Alzheimerio liga – atminties ir kalbos.

Raktažodžiai: Alzheimerio liga, Levi kūnelių liga, Taisytas Adenbruko kognityvinis tyrimas, neurodegeneracinės ligos, judėjimo sutrikimai, kognityviniai simptomai, neuropsichologinis įvertinimas.