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

A. Rotomskis*
A. Grabauskaitë**
R. Margevičiūtë***
A. Germanavičius****
G. Kaubrys*****
G. Jagelavičiūtë******
A. Žimkus*******
N. Piraškevičiūtë*******
J. Račkauskaitë*******

*Vilnius University,
Faculty of Philosophy,
Department of Clinical and Organizational Psychology

**Vilnius University, Faculty of Natural Science,
Department of Neurobiology and Biophysics

***University of Edinburgh,
School of Philosophy, Psychology and Language Sciences,
Centre for Clinical Brain Sciences

****Vilnius University, Faculty of Medicine,
Clinic of Psychiatry

*****Vilnius University,
Faculty of Medicine, Clinic of Neurology and Neurosurgery

******Vilnius University,
Faculty of Philosophy,
Department of General Psychology

*******Vilnius University,
Faculty of Medicine

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.

Neurologijos seminarai 2015; 19(63): 59–63

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

Adresas:
Augustinas Rotomskis
Vilnius University, Faculty of Philosophy
Department of Clinical and Organizational Psychology
Universiteto g. 9/1, LT-01513 Vilnius
Tel. (+370 5) 2667605, e-mail: rotomskis.augustinas@gmail.com
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-RLT) is able to detect dementia. Nevertheless, no further research using ACE-RLT, 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 nervous 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 fulfilled 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-RLT). The ACE-RLT 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
Validation of Addenbrooke’s Cognitive Examination-Revised for the Differential Diagnostics of Dementia with Lewy Bodies...

Table 1. Demographic Characteristics of the Patient and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>AD</th>
<th>DBL</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>% females</td>
<td>64.9%</td>
<td>63.5%</td>
<td>60.0%</td>
<td>64.6%</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>66.03 (±8.67)</td>
<td>65.58 (±7.21)</td>
<td>63.63 (±7.11)</td>
<td>67.24 (±10.07)</td>
</tr>
<tr>
<td>Years of Education (SD)</td>
<td>11.93 (±2.81)</td>
<td>11.83 (±3.11)</td>
<td>11.73 (±2.75)</td>
<td>12.07 (±2.58)</td>
</tr>
</tbody>
</table>

Note. SD: Standard deviation

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 (χ², 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 effect, while gender did not (F=0.779; Beta=0.075; p=0.438).

Validity and reliability of the ACE-RLT. Two methods were used to calculate the validity of ACE-RLT. We carried out a logistic-regression analysis to evaluate the ACE-RLT 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-RLT score correctly classified 99.5% of the cases. We also carried ROC analysis to evaluate ACE-RLT ability to discriminate the dementia group. The trade-off between sensitivity (true positive rate) and 1-specificity (false positive rate) of the ACE-RLT 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-RLT 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-RLT 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-RLT (score below the recommended cut-off of 74 points) significantly more often than controls (χ² test; 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 of 74 points for dementia. Reliability of the ACE-RLT was measured in terms of internal consistency, using Cronbach’s alpha coefficient. The Cronbach’s alpha for the ACE-RLT was 0.912 (0.8 is considered excellent).

Differentiating AD and DLB. Mann-Whitney U-test was used to compare ACE-RLT 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

Table 2. Comparison of mean scores of AD group and DLB group on components of ACE-RLT (in parenthesis SD)

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>DLB</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>6.548 (±2.06)</td>
<td>6.767 (±1.28)</td>
<td>0.95</td>
</tr>
<tr>
<td>Attention</td>
<td>5.247 (±1.26)</td>
<td>5.367 (±1.36)</td>
<td>0.572</td>
</tr>
<tr>
<td>Memory</td>
<td>7.973 (±3.18)</td>
<td>12.833 (±2.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>4.904 (±2.59)</td>
<td>3.3 (±1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Language</td>
<td>17.548 (±3.95)</td>
<td>22.2 (±1.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>11.548 (±2.56)</td>
<td>7.5 (±1.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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.

### Acknowledgement

This work was partly supported by the project “Promotion of Student Scientific Activities” (VP1-3.1-ŠMM-01-V-02-003) from the Research Council of Lithuania (AR). This project is funded by the Republic of Lithuania and European Social Fund under the 2007–2013 Human Resources Development Operational Programme’s priority 3.

The data was partly collected by psychology students from the Lithuanian psychology students association Scientific branch.
REFERENCES


A. Rotomskis, A. Grauksaitė, R. Margiavičiūtė, A. Germanavičius, G. Kaubrys, G. Jagelavičiūtė, A. Žimkus, N. Piraškevičiūtė, J. Račkauskaitė

ADENBRUKO KOGNITYVINIO TYRIMO TAISYTO METODIKOS VALIDACIJA DIFERENCIINEI LEVI KŪNELIŲ IR ALZHEIMERIO LIGŲ DIAGNOSTIKAI LIETUVIŠKAI KALBANČIOJE POPULIACIJOJE

Santrauka


Šio tyrimo tikslas yra patikrinti, kaip ACE-R_LT diferencijuoją Alzheimero ir Levi kūnelių ligas.


Rezultatai. Alzheimero ligos grupėje ne tiriamųjų amžiaus (p = 0,060), nei lyties (p = 0,466), nei išsilavinimo (p = 0,206) po veikis ACE-R rezultatams nebuvo pateikti. Levi kūnelių grupėje nei tiriamųjų amžiaus (p = 0,249), nei lyties (p = 0,206), nei išsilavinimo (p = 0,615) po veikis ACE-R rezultatams nebuvo pateikti. Kontrolinėje grupėje pateiktas amžiaus (p < 0,001), ir išsilavinimo (p < 0,001) po veikis ACE-R rezultatams, bet lyties sąsąsios su rezultatais nebuvo nustatytos (p = 0,438). Šiam tyrimo ACE-R_LT pasižymėjo itin aukštu patikimumu (Kronbacho α = 0,912).

Ribinių normos įvertinę buvo pasirinkti Alzheimero ligai apiktin anksstesnių tyrėjų pasirūpinti 74 balų. Šiam tyrimo nustatytas ACE-R_LT 100 % jautrumas ir 90,5 % specifika. AD grupės balai atminties ir kalbos subklaše statistiškai reikšmingai mažesni negu ribinis normos įvertis ir DBL grupės balai (chi-kvadrato kriterijus, p < 0,0001). DBL grupė surinko statistiškai reikšmingai mažiau balų negu rekomenduojamas ribinis normos įvertis, palyginus su AD, žodinio sklendumo erdvinų gebėjimų subklaše (chi-kvadratas, p < 0,0001).


Raktąžodžiai: Alzheimero liga, Levi kūnelių liga, Taisytas Adenbruko kognityvinis tyrimas, neurodegeneracinės ligos, judėjimo sutrikimai, kognityvinių simptomai, neuropsichologinis įvertinimas.

Gauta: 2014 10 10
Priima spaudai: 2014 12 13