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# Differential Diagnostics of Dementia with Lewy Bodies and Parkinson's Disease with Dementia Using Addenbrooke's Cognitive Examination-Revised in Lithuanian-speaking Population

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**Summary.** *Background.* An assessment of cognitive functioning is considered to be valuable in differential diagnostics of movement disorders. Several studies showed that Addenbrooke's Cognitive Examination-Revised (ACE-R) is an accurate tool in detecting dementia in Parkinson's and related diseases. It is still quite difficult to distinguish between Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD). The aim of this study is to investigate the ability of Addenbrooke's Cognitive Examination-Revised to differentiate mild-moderate dementia with Lewy bodies from Parkinson's disease with mild-moderate dementia in Lithuanian-speaking population.

*Methods.* The Lithuanian version of Addenbrooke's Cognitive Examination-Revised (ACE-R<sup>LT</sup>) was applied individually to 30 patients with mild-moderate dementia with Lewy bodies, 34 patients with Parkinson's disease dementia, and 64 controls, who were matched for age, gender and education. By using ACE-R<sup>LT</sup>, the following cognitive domains were evaluated: orientation, attention, memory, verbal fluency, language, and visuospatial abilities; the higher score, the better performance. For statistical analysis, one-way ANOVA, Mann-Whitney U test, and binary logistic regression were done.

*Results.* The statistical analysis yielded no significant difference among three groups of participants in age ( $p=0.036$ ), years of education ( $p=0.401$ ), and gender ( $\chi^2$ ,  $p=0.048$ ). The ACE-R<sup>LT</sup> appeared to be good enough in prognosticating dementia ( $Ex(B)=0.828$ ,  $\chi^2=84.171$ ,  $p=0.000$ ), with 84% of overall correct cases. While comparing two groups with different diseases, DLB patients had lower scores in overall cognitive performance on ACE-R (DLB average score was 58 and PDD average score was 70,  $p=0.000$ ). The DLB group had lower scores compared to PDD in those particular cognitive domains: orientation (6.8 points for DLB and 8.7 for PDD), attention ( $5.4<6.7$ ), verbal fluency ( $3.3<7.2$ ), and visuospatial abilities ( $7.5<12.4$ ); for each domain,  $p=0.000$ .

*Conclusions.* The ACE-R<sup>LT</sup>, an accurate tool in prognosticating dementia, showed only mild differences between DLB and PDD. In line with former studies, the only difference between the DLB and PDD cognitive functioning was that DLB had more severe impairments. Whether DLB and PDD is the same entity or not, remains an open question suggesting the need for more research in this field using different tasks for the cognitive evaluation.

**Keywords:** Lewy body disease, Parkinson's disease dementia, movement disorders, cognitive symptoms, neuropsychological assessment.

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## BACKGROUND

Significance of cognitive dysfunction in movement disorders is often underestimated [1]. Nevertheless, cognitive and motor functions are related because of common underlying mechanisms, basal ganglia, and cerebellar loops [2,

3]. As different movement disorders produce different cognitive profiles [4], a cognitive evaluation in such diseases seems to be valuable. In addition, neurophysiological markers combined with cognitive assessment can provide better prognosis of disease course, compared to using only one method of evaluation [5]. Observing cognitive functions in movement disorders is also important as cognitive dysfunction may reduce the quality of life, as indicated in Parkinson's disease (PD) patients [6].

Among movement disorders, there is a difficult task to distinguish between Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) [7]. The diagnosis of DLB requires recurrent fully formed visual hal-

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lucinations, parkinsonism (bradykinesia, rigidity, tremor), and fluctuating cognition [8]. Parkinson's disease dementia has symptoms of PD, plus, a cognitive impairment severe enough to disturb daily life and motor symptoms of PD is usually developed prior to the onset of dementia [9]. Lewy bodies (intraneuronal aggregates of misfolded alpha-synuclein) are the pathologic hallmarks of both diseases [10]. In general, PDD and DLB share many neurobiological similarities [11]. There is still a lot of debate whether DLB and PDD are distinct diseases or simply the same illness with different time courses of presentation of cognitive symptoms relative to motor symptoms [10–12]. Some authors even tend to consider DLB and PDD together as the same pathology using an umbrella term Lewy body disease (LBD) [10, 13].

Other authors emphasize a need to differentiate between those diagnoses, stating that an accurate diagnosis is crucial given differences in progression, prognosis, and treatment of these [14]. There is a great need of a definitive diagnosis both for consideration of therapeutic options and informing patients, their family and caregivers about expected clinical progression and disease course [15]. Furthermore, the diagnosis for a patient can come as a relief, because it provides an explanation for symptoms and may offer the possibility for symptomatic treatment [16].

Some scientists try to find differences in cognitive functioning between the DLB and PDD patients. One of the first related attempts was published in the previous century, considering differences of cognitive profiles between PD, DLB and AD [17]. For the cognitive evaluation, authors used Mini Mental State Examination (MMSE), Clinical Dementia rating (that is an interview and some checklists), digit span (for auditory attention and short term memory), verbal and category fluency (to assess the access to semantic information under time constraint), clock face (for visuospatial functioning), and Nelson card sort test (to assess the patient's ability to develop new concepts and shift sets). They found that DLB and AD patients, in comparison with PD patients, showed more deficiencies in the performance of MMSE, digit span, verbal fluency, Nelson card sort, and clock face test. There was another interesting finding: although AD, PD patients and controls all performed in clock copying task better than in drawing, it was not a case in DLB patients. For patients with DLB, it was easier to draw a clock showing the denoted time than to copy the same picture of the clock that is already drawn. The limitation of the research was that authors did not mention, whether the patients with PD also had a diagnosis of dementia.

Nonetheless, the subsequent studies also revealed the more evident cognitive impairments in DLB compared to PDD, considering such domains as: attention (digit span task), episodic verbal memory and executive functions (Stroop task) from the test battery of the Seoul Neuropsychological Screening [18]; a conceptualisation task from the Mattis dementia rating scale [19]. In contrast, some authors did not manage to find any difference in cognitive tasks between DLB and PDD, using a test battery con-

sisting of orientation, verbal and nonverbal memory, verbal and nonverbal reasoning, auditory comprehension, repetition, attention, and visuoconstructional and visuo-perceptual skills [11]. Finally, one of the most recent reviews summarizes that the DLB and PDD can be distinguished from each other by worse performance of patients with DLB (in comparison to patients with PDD) in the following cognitive domains: memory, visuospatial ability, attention, processing speed, and executive functions [14].

In Lithuania, the most recently standardized test for dementia screening is Addenbrooke's Cognitive Examination-Revised (ACE-R<sup>LT</sup>) [20]. It is a brief, inexpensive and easy to administer test, consisting of five sub-scores: orientation/attention; memory; verbal fluency; language, and visuospatial [21, 22]. Different research has proven ACE-R and its previous version ACE validity in diagnosing dementia in PD (ACE-R: [23, 24], ACE: [9, 25]). The validity of ACE-R in diagnosing DLB was verified by the authors of the test [21] and also by Lithuanian authors in Lithuanian population [26]. However, a study in which DLB and PDD would be compared using ACE-R is still lacking.

## OBJECTIVE

The aim of this study was to investigate the ability of Addenbrooke's Cognitive Examination-Revised to differentiate mild-moderate dementia with Lewy bodies from mild-moderate Parkinson's disease with dementia in Lithuanian-speaking population.

## METHODS

### Participants

The following participants were recruited: 34 patients with mild-moderate PDD, 30 patients with mild-moderate DLB, and 64 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 or other primary nervous system diseases, an acute stroke, primary psychiatric disorder, 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 matched for age and years of education. Although there were more women in DLB group and less in PDD, the control group and the group with dementias were matched in terms of gender. All of the patients in the PDD group fulfilled Movement Disorder Society Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease [27]. All of the patients in the DLB group fulfilled Consortium on Dementia with Lewy bodies established

criteria for probable DLB at the time of testing [28]. Spouses or friends of the participating patients were recruited as healthy controls having scores  $\geq 27$  points on the MMSE [29]. All participants had sufficient knowledge of the Lithuanian language to participate in the study. All of the 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**

The Lithuanian version of Addenbrooke’s Cognitive Examination-Revised (ACE-R<sup>LT</sup>) was applied for the evaluation of each participant individually. The ACE-R<sup>LT</sup> takes about 20–40 minutes to administer and score in a clinical setting. It contains five sub-scores: orientation/attention (18 points, 10 for orientation and 8 for attention), memory (26 points), verbal fluency (14 points), language (26 points), and visuospatial (16 points). ACE-R<sup>LT</sup> maximum score is 100, composed by the addition of all domains.

**Statistical analysis**

For the statistical analysis, *IBM SPSS (Statistical Package for Social Sciences) 20.0* was used. To assess the ACE-R’s ability in prognosticating dementia, the *binary logistic regression analysis* was applied. The *Mann-Whitney U* test for the two samples (i.e. between two different diseases, PDD and DLB) and *one-way ANOVA* for the three samples were used, as the data from all of the scales did not match a normal distribution (by *Shapiro-Wilk* test,  $p=0.000$ ) and the groups were independent one from another. For categorical variables, the *Chi Square* was used. The level of statistical significance  $\alpha=0.01$  was chosen for all of the computations.

**RESULTS**

**Demographics**

Demographic characteristics of the patient and control groups are summarized in Table 1. The groups were matched for age (*one-way ANOVA*,  $F=3.401$ ;  $p=0.036$ ), years of education (*one-way ANOVA*,  $F=0.920$ ;  $p=0.401$ ), and gender ( $\chi^2$ ,  $p=0.048$ ).

**The ability of ACE-R<sup>LT</sup> to prognosticate dementia**

The ACE-R<sup>LT</sup> appeared to be good enough in prognosticating dementia (*binary logistic regression*,

$Ex(B)=0.828$ ,  $\chi^2=84.171$ ,  $p=0.000$ ), with 84% of overall correct cases. The percentage of correct attribution was higher for the non-dementia cases (89%) in comparison to the dementia cases (80%). The *Cox & Snell R Square* was 0.482 and *Nagelkerke R Square* was 0.643.

**Differentiating PDD and DLB**

Series of *Mann-Whitney U* tests revealed statistical significant mean differences ( $p=0.000$ ) between the orientation, attention, verbal fluency, visuospatial, and general ACE-R scores (Table 2) of PDD and DLB groups. In all of previously mentioned cognitive domains as well as in general cognitive functioning, DLB showed greater impairments compared to PDD group.

**DISCUSSION**

Although the difference did not reach a statistical significance ( $p=0.036$ , while  $\alpha=0.01$ ), the age of different disease groups was not identical, the PDD group was in average older (69.3 years) than DLB (63.6). It may not be a surprise, knowing that in PD the diagnosis of dementia comes later than in DLB [19], so the younger patients with DLB are more available for the research, in comparison with PDD. The tendency of DLB patients to be younger than PDD patients was also confirmed by the incidence study in Olmsted County, Minnesota, that included a 15-year analysis of parkinsonian cases (with the total number 64 of DLB and 46 PDD patients) [30].

Also, the demographics revealed that the distribution of different genders in different diseases was not perfectly equal (although, still without a statistically significant difference). In the present study, the rate of woman was

Table 1. **Demographic Characteristics of the Patient and Control Groups** (in parenthesis standard deviation)

	Total	PDD	DLB	Controls
% females	43.8	29.4	60.0	43.8
Mean age in years	66.8 (8.8)	69.3 (8.9)	63.6 (7.1)	67.0 (9.1)
Years of education	11.9 (2.8)	12.5 (3.0)	11.7 (2.8)	11.7 (2.8)

Table 2. **Comparison of mean scores of PDD group and DLB group on components of ACE-R<sup>LT</sup>** (in parenthesis standard deviation)

	PDD	DLB	p value
Orientation (maximum 10)	8.740 (1.639)	6.770 (1.278)	0.000
Attention (maximum 8)	6.710 (2.038)	5.370 (1.351)	0.000
Memory (maximum 26)	13.794 (5.098)	12.830 (2.151)	0.324
Verbal fluency (maximum 14)	7.177 (3.554)	3.300 (1.179)	0.000
Language (maximum 26)	21.029 (4.436)	22.200 (1.937)	0.765
Visuospatial (maximum 16)	12.412 (3.105)	7.500 (1.852)	0.000
General ACE-R score (maximum 100)	69.853 (17.424)	57.967 (4.130)	0.000

Note: grey fill demonstrates a statistical significant difference, i.e.  $p<0.01$

higher in DLB group (60%) and there was a deficiency of them in the PDD group (29%). Conversely, in the previously mentioned incidence study [30], men had higher incidence rate of DLB than women. And in PDD, in their study, the overall incidence was similar in men and women. This contraposition may be explained by the fact that the samples in both research were quite small. Considering a possible gender influence on the results of cognitive tests, it was previously showed that gender did not have an impact on ACE-R<sup>LT</sup> performance neither in healthy, nor in AD, nor in DLB group [26].

Regarding the ACE-R<sup>LT</sup> ability to detect dementia, the previous investigations were extended. In the first article on ACE-R<sup>LT</sup> adaptation in Lithuania, with the cut-off point 74 (the total score of the test) for dementia, the sensitivity of the tool was 65% and specificity 99%. Together with findings from the present study (a good ability to prognosticate dementia), the ACE-R<sup>LT</sup> seems to be a valuable test for the dementia screening.

In line with the previous findings, see [14] for the review, the present study found more evident cognitive decline in DLB patients, compared to PDD. The next step is to look through all the findings in different cognitive domains. First of all, the ACE-R<sup>LT</sup> scale for *orientation* indicated a more severe decline in DLB, compared to PDD, and this is the same result that was shown by other authors [11], the same is true for *attention* [18]. The previous authors also found a greater impairment in *verbal fluency* and *visuospatial* abilities in DLB, compared to PD (PD not necessarily with dementia) [17], and the present study extended those results by showing the same tendency even if the Parkinson's disease patients were also demented. In contrast with the former investigations [18], the present study was not able to prove any difference in the *memory* domain. The inconsistency of two different studies could be explained by some different tools used to evaluate a construct of memory. In the cited research, three-word registration and recall, and Seoul Verbal Learning Test (by its design, the task allowed for the anterograde memory testing) were used. The ACE-R also includes a task of three-word registration and recall, plus a task for the anterograde memory with the request to recall and recognize an address, and a task with some questions to test the state of the retrograde memory. So the main difference of ACE-R memory scale is an inclusion of a retrograde memory evaluation. In the present study, although the overall memory score was higher in the patients with PDD compared to DLB (without a statistical significant difference, see table 2), the score in a task of the retrograde memory was higher in DLB (for DLB: 3.16, for PDD: 2.85, no statistical significant difference again, *Man-Whitney U* test,  $p=0.339$ ). The different courses of the scores belonging to different memory aspects may have summated, and in result, one may not see any difference at all. In the future studies, we suggest to pay more attention to a retrograde versus anterograde memory aspects while comparing DLB and PDD. The ACE-R may be found as a better tool in evaluating mem-

ory as it contains both the anterograde and retrograde memory giving the better comprehension of the individual's overall memory state in comparison with the Seoul Verbal Learning Test [19]. However, a more precise evaluation of a retrograde memory is still needed as ACE-R includes only one task with total four items in it with possibility to get 0, 1, 2, 3 or 4 scores (that is, too few different variants to get a statistically significant results, especially if the samples of the patients are quite small). Finally, the *language* scale in the present study indicated that the language domain (except the verbal fluency) did not help in distinguishing between the diagnosis of DLB and PDD, and this result was consistent with the former studies, e.g. [18, 31].

To sum up, at first glance, the present study shows only mild differences between DLB and PDD regarding the cognitive functioning. Namely, the same cognitive domains in both diseases are affected but in DLB they are always affected more, compared to PDD. So we still do not have the tools to deny a claim that "PDD and DLB neuropsychological profiles share sufficient similarity to resist accurate and reliable differentiation. <...> By and large, the commonalities between the neuropsychological profiles of DLB and PDD outweigh the differences" [32]. And the greater impairments in DLB may only be a manifest of the tendency for the diseases to become more severe if they had an earlier time of onset, as the dementia in the DLB is by default always diagnosed earlier in the course of the disease, compared to the case of PDD [33]. On the other hand, there is still a possibility to find some qualitative differences between the cognitive performance in DLB and PDD, such as different performance of the two clock face tasks [17] or the possibly different capacities of retrograde and anterograde memory in each of the diseases. Thus, we suggest that more research in the field of cognitive based differential diagnostics of DLB and PDD, using different neuropsychological instruments, should be done.

## CONCLUSIONS

1. The Lithuanian version of Addenbrooke's Cognitive Examination-Revised was shown to be accurate in prognosticating dementia (*binary logistic regression*,  $\text{Ex(B)}=0.828$ ,  $\chi^2=84.171$ ,  $p=0.000$ ).
2. Patients with Parkinson's disease dementia showed better performance in overall Addenbrooke's Cognitive Examination-Revised test (average score for Parkinson's disease dementia was 69.85 and for Dementia with Lewy bodies group it was 57.97, *Man-Whitney U* test,  $p=0.000$ ).
3. The dementia with Lewy bodies patients, compared to the Parkinson's disease with dementia patients, had more severe impairments in the following cognitive domains: orientation, attention, verbal fluency, and visuospatial abilities (*Man-Whitney U* test,  $p=0.000$ ).

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**PARKINSONO LIGOS SU DEMENCIJA IR LEVI  
KŪNELIŲ LIGOS DIFERENCINĖ DIAGNOSTIKA,  
TAIKANT TAISYTA ADENBRUKO KOGNITYVINIO  
TYRIMO METODIKĄ LIETUVIŠKAI KALBANČIOJE  
POPULIACIJOJE**

**Santrauka**

*Ivadas.* Esant judėjimo sutrikimams, naudingas ir kognityvinis paciento įvertinimas. Ankstesniais tyrimais įrodytas Taisyto Adenbruko kognityvinio tyrimo (ACE-R) tinkamumas nustatyti demencijai sergant Parkinsono ir susijusiomis ligomis. Iki šiol kyla sunkumų tarpusavyje diferencijuojant Parkinsono ligą su demencija (PDD) ir Levi kūnelių ligą (DLB). Šio tyrimo tikslas yra patikrinti, kaip Taisyta Adenbruko kognityvinio tyrimo metodika diferencijuoja Parkinsono ligą su demencija ir Levi kūnelių ligą lietuviškai kalbančioje populiacijoje.

*Tiriamieji ir tyrimo metodai.* Tyrime dalyvavo 30 DLB, 34 PDD pacientai ir 64 kontrolinės grupės tiriamieji. Pastarosios

grupės tiriamieji parinkti taip, kad nei pagal amžių, nei pagal lyčių procentą, nei pagal išsilavinimo trukmę statistiškai reikšmingai nesiskirtų nuo pacientų grupių. Su kiekvienu iš tiriamųjų individui buvo atlikta Taisyto Adenbruko kognityvinio tyrimo metodikos lietuviška versija (ACE-R<sup>LT</sup>). Minėtu testu įvertinamos šios sritys: orientacija, dėmesys, atmintis, žodinis sklandumas, kalba ir erdviniai gebėjimai. Didėsnis įvertis reiškia geresnę atliktą. Statistinei analizei naudota vienfaktorinė dispersinė analizė ANOVA, dvinarė logistinė regresija ir Mano-Vitnio U kriterijus.

*Rezultatai.* Tarp trijų tiriamųjų grupių nebuvo statistiškai reikšmingo nei amžiaus ( $p = 0,036$ ), nei lyčių procento ( $\chi^2$ ,  $p = 0,048$ ), nei išsilavinimo trukmės ( $p = 0,401$ ) skirtumo. Taisytos Adenbruko kognityvinio tyrimo metodikos lietuviška versija gana gerai aptinka demenciją ( $Ex(B) = 0,828$ ,  $\chi^2 = 84,171$ ,  $p = 0,000$ , su 84 % teisingų prognozuotų atvejų). Tarp tirtų ligų statistiškai reikšmingi skirtumai užfiksuoti bendrame testo įvertyme (DLB vidutiniškai surinko 58 balus, PDD – 70), orientacijos ( $6,8 < 8,7$ ), dėmesio ( $5,4 < 6,7$ ), žodinio sklandumo ( $3,3 < 7,2$ ) ir erdviųjų gebėjimų ( $7,5 < 12,4$ ) skalėse;  $p = 0,000$ .

*Išvados.* Nors ACE-R<sup>LT</sup> gerai tinka aptikti demencijai, tačiau šio testo rezultatai rodo tik nedidelius skirtumus tarp DLB ir PDD pacientų kognityvinio funkcionavimo. Būtent, vertinant skirtingas kognityvines sritis, DLB pacientai pasižymi labiau išreikštais sutrikimais. Tas pats būdinga ir ankstesnių tyrėjų rezultatams, todėl vis dar išlieka klausimas, ar DLB ir PDD yra skirtingos patologijos. Siekiant prisidėti prie atsakymo į šį klausimą, siūloma atlikti daugiau tyrimų, taikant įvairesnes kognityvines užduotis.

**Raktažodžiai:** Levi kūnelių liga, Parkinsono liga su demencija, judėjimo sutrikimai, kognityviniai simptomai, neuropsichologinis įvertinimas.

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