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# Sensitivity and specificity of Addenbrooke's Cognitive Examination, Mattis Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State Examination for diagnosing dementia in Parkinson's disease

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ABSTRACT

*Introduction:* Among the non-motor features of Parkinson's disease (PD), cognitive impairment is one of the most troublesome problems. Highly sensitive and specific screening instruments for detecting dementia in PD (PDD) are required in the clinical practice.
*Methods:* In our study we evaluated the sensitivity and specificity of different neuropsychological tests (Addenbrooke's Cognitive Examination, ACE; Frontal Assessment Battery, FAB and Mattis Dementia Rating Scale, MDRS) in 73 Parkinson's disease patients without depression. By receiver operating characteristic curve analysis, these screening instruments were tested against the recently established clinical diagnostic criteria of PDD.
*Results:* Best cut-off score for ACE to identify PDD was 80 points (sensitivity = 74.0%, specificity = 78.1%). For FAB the most optimal cut-off value was 12 points (sensitivity = 66.3%, specificity = 72.2%); whereas for MDRS it was 125 points (sensitivity = 89.8%, specificity = 98.3%). Among the examined test batteries, MDRS had the best clinicometric profile for detecting PDD.
*Conclusion:* Although the types of applied screening instruments might differ from movement disorder clinic to clinic within a country, determination of the most specific and sensitive test for the given population remains to be an important task. Our results demonstrated that the specificity and sensitivity of MDRS was better than those of ACE, FAB and MMSE in Hungary. However, further studies with larger sample size and more uniform criteria for participation are required to determine the most suitable screening instrument for cognitive impairment.



## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by both motor and non-motor symptoms including depression, fatigue and vegetative problems. Among non-motor features, cognitive impairment has one of the most serious consequences by limiting the quality of life and requiring increased caregiver's burden [1–5]. Detection of dementia in Parkinson's disease (PDD) [6] is of high importance, because cognitive decline is a frequent and important excluding criteria for deep brain stimulator (DBS) implantation [7]. Therefore, the necessity of proper screening for cognitive impairment in PD is highly encouraged in the clinical practice.

Currently, Mini Mental State Examination (MMSE) is the most commonly used tool for measuring cognitive abilities in Hungary [8,9]. Although it can evaluate orientation, memory, visual abilities, attention and calculation, language, writing, reading, and constructive capabilities, it is not sensitive enough for identifying frontal and executive deficits, and visuospatial dysfunctions. Moreover, it has poor sensitivity for detecting dementia in early stages [10,11] and it is also unable to differentiate between major types of dementia. Although MMSE has been translated and validated into many languages and used in many countries [12]; it remains unsuitable for judging eligibility for deep brain stimulation of the subthalamic nuclei (STN DBS) [13].

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Therefore, other dementia screening tests are needed in the clinical practice. Addenbrooke's Cognitive Examination (ACE) is able to detect early stages of dementia and differentiate some subtypes that typically occur in Alzheimer's disease (AD) and frontotemporal dementia (FTD). This is done by using a subscore called VL/OM ratio that stands for (verbal fluency + language)/(orientation + delayed recall). It is based on the observation that patients with AD perform better than patients with FTD in verbal fluency and language tasks [14]. ACE also evaluates the major domains of PDD such as orientation, attention and mental flexibility, episodic and semantic memory, verbal fluency, phonemic and semantic category, aphasia tasks, visuospatial and constructional ability; however, it was initially developed for screening AD. The maximal achievable score on ACE is 100 points. ACE was translated into many languages including Hungarian, but it has only been tested in AD and not in PD. Although ACE was validated in PD in some countries, it has not been compared with the newly established and validated clinical criteria of PDD yet [15].

Mattis Dementia Rating Scale (MDRS) is also a widely used screening instrument for dementia. It can measure the domains of attention, initiation and perseveration, construction, conceptualization and memory. MDRS seems to be sensitive for mediotemporal and frontal pathology [17,18]. As far as the authors are aware of it is a frequently used screening tool for judging cognitive impairment in European DBS centers [19]. Its maximum obtainable score is 144; whereas, the cut-off scores for dementia in French and Spanish PD population was 130 and 123, respectively [19,20].

Previously MDRS has not been translated and validated in Hungary. The authors of the present article performed the formal lingual translation and verification before initiating this study.

Frontal Assessment Battery (FAB) is a very short tool for evaluating frontal pathology by measuring six subscales: conceptualization and abstract thinking (similarities), mental flexibility (lexical fluency), motor series/programming (Luria's fist-edge-palm test), conflicting instructions (sensitivity to interference), go-no-go (inhibitory control), and prehensive behavior (environmental autonomy) [21]. This test is proven to be able to differentiate between frontotemporal dementia and AD [22,23]; however, its usability in PDD has not been evaluated in details yet.

In this study we compared the sensitivity and specificity of ACE, MDRS, FAB, and MMSE in the respect to the newly established clinical diagnostic criteria of PDD [6]. Our aim was to validate and compare these dementia screening tests on the cognitive profile in Hungarian idiopathic PD patients.

## 2. Methods

### 2.1. Participants

One hundred and two consecutive PD patients treated at Department of Neurology, University of Pécs, were recruited for this study. Each patient fulfilled the clinical diagnostic criteria for idiopathic PD [24]. All of the subjects gave a written informed consent according to the approval of the Regional Ethical Board of University of Pécs.

History of cerebrovascular disease, alcoholism or other conditions known to impair mental status besides PD served as exclusion criteria for participation. Each patient had a routine brain MRI and patients with focal abnormalities on neuroimaging studies, abnormalities in thyroid hormone levels, or noncompensated systemic diseases (i.e. diabetes, hypertension, heart failure) were also excluded.

### 2.2. Patient evaluation

Patients were evaluated using Hungarian version of Montgomery-Asberg Depression Rating Scale (MADRS) [25], MMSE [9], ACE [14,16], MDRS [17] and FAB [21]. Severity of the Parkinsonian symptoms was assessed by the modified Hoehn-Yahr (HYS) [26] and Unified Parkinson's Disease Rating Scales (UPDRS) [27].

Depressed patients were excluded from clinical investigation (score > 18 on MADRS and/or fulfilling the criteria of DSM-IV-TR for depression) to minimize the impact of affective syndromes on cognitive performance.

Afterwards, the non-depressed PD patients were divided into two groups based on the fulfillment of the clinical diagnostic criteria of PDD: patients with PDD (PDD + group) and patients without PDD (PDD − group) [6].

### 2.3. Data analysis

Statistical analyses were performed by IBM SPSS software package (version 19, SPSS Inc, MN). Because most data followed the normal distribution, parametric tests (non-paired *t*-test and Pearson's correlation test) were applied. Since HYS and sex are categorical and dichotomous variable, Pearson Chi–Square and Kendall-tau tests were applied for analyses involving HYS and sex. To measure specificity and sensitivity for neurocognitive batteries, Receiver Operating Characteristic (ROC) curve analysis was obtained. The level of significance was set at .05.

## 3. Results

Twenty-nine patients had a coexistent depression; therefore, they were excluded from further analyses. Out of the 73 evaluated subjects, only 22 fulfilled the clinical diagnostic criteria for PDD (PDD+). The comparison of the demographic and clinical characteristics between PDD+ and PDD− groups is presented in Table 1. The major demographic properties (e.g. age, education, sex, disease duration and age of onset), the severity of Parkinsonian symptoms (UPDRS, HYS, ADL) and the applied dose of dopaminergic medication did not differ significantly between these groups. Fulfilling our expectations, all the examined dementia scales (MDRS, FAB, VLOM, and ACE) demonstrated significant differences between the PDD+ and PDD− groups.

Significant correlations between scores of obtained tests and various clinical parameters are demonstrated in Table 2. Out of the evaluated dementia screening tests, only the ACE showed a slight, but significant correlation with the age of the patients. However, the major clinical parameters describing Parkinsonian symptoms (e.g. UPDRS, HYS, and ADL), depression (MADRS), and disease

**Table 1**
Comparison of clinical characteristics and the results of obtained tests between the PD patients with dementia (PDD+) and without dementia (PDD−).

| | PDD+ ($n = 51$) | | PDD− ($n = 22$) | | Significance |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 62.7 | 8.4 | 64.6 | 10.6 | NS |
| Sex (M/F)[a] | 36/15 | | 18/4 | | NS[a] |
| Education (years) | 11.9 | 4.4 | 12.3 | 3.1 | NS |
| Age of onset (years) | 52.8 | 10.1 | 54.1 | 9.8 | NS |
| Disease duration (years) | 8.3 | 4.8 | 8.3 | 4.7 | NS |
| UPDRS1 | 2.6 | 6.0 | 2.1 | 3.0 | NS |
| UPDRS2 | 15.6 | 8.2 | 19.2 | 10.6 | NS |
| UPDRS3 | 34.7 | 14.7 | 38.1 | 15.2 | NS |
| UPDRS4 | 5.2 | 4.9 | 4.1 | 4.2 | NS |
| HYS[a] | 2.5 | | 2.5 | | NS[a] |
| ADL | 81.7 | 10.2 | 78.5 | 10.1 | NS |
| Levodopa equivalent dose (mg) | 964.9 | 463.8 | 925.7 | 425.6 | NS |
| MADRS | 9.2 | 6.2 | 9.1 | 4.9 | NS |
| MMSE | 28.4 | 1.2 | 23.5 | 2.1 | $p < .01$ |
| FAB | 14.1 | 2.2 | 10.4 | 2.5 | $p < .01$ |
| ACE | 86.1 | 6.1 | 73.0 | 10.1 | $p < .01$ |
| VLOM | 2.8 | .5 | 3.0 | .4 | $p < .05$ |
| Attention subscore of MDRS | 35.6 | 1.1 | 34.9 | 1.5 | $p < .05$ |
| Initiation subscore of MDRS | 35.4 | 2.4 | 30.5 | 4.4 | $p < .01$ |
| Construction subscore of MDRS | 6.0 | .2 | 5.6 | 1.4 | NS |
| Conceptualization subscore of MDRS | 37.7 | 1.9 | 36.8 | 3.4 | NS |
| Memory subscore of MDRS | 22.0 | 2.0 | 18.6 | 3.4 | $p < .05$ |
| Total score of MDRS | 136.8 | 4.2 | 122.9 | 6.9 | $p < .01$ |

Abbreviations: ACE: Addenbrooke's Cognitive Examination; ADL: Activities of Daily Living; FAB: Frontal Assessment Battery; HYS: modified Hoehn & Yahr Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental State Examination; SD: standard deviation; UPDRS3: Unified Parkinson's Disease Rating Scale part 3 –motor examination. VLOM: verbal fluency + language/orientation + memory.

[a] Paired-*t* tests, except for HYS and sex (Pearson Chi–Square test).

**Table 2**
Correlation coefficients between various clinical parameters and the results of the dementia rating tests.

| | MMSE | FAB | ACE | VLOM | Total score of MDRS | Age | Disease duration | MADS | UPDRS3 | HYS | ADL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MMSE | 1 | **.419**[b] | **.717**[b] | **−.251**[a] | −.023 | −.099 | .163 | −.139 | −.039 | .101[+] | .040 |
| FAB | **.419**[b] | 1 | **.556**[b] | −.176 | .006 | −.230 | .103 | .015 | −.230 | .018[+] | .177 |
| ACE | **.717**[b] | **.556**[b] | 1 | **−.406**[b] | .111 | **−.317**[b] | .216 | −.021 | −.121 | .115[+] | .034 |
| VLOM | **−.251**[a] | −.176 | **−.406**[b] | 1 | −.105 | **.255**[a] | .102 | .212 | −.237 | .000[+] | −.018 |
| Total score of MDRS | −.023 | .006 | .111 | −.105 | 1 | .157 | .225 | .059 | −.175 | .086[+] | .154 |
| Age | −.099 | −.230 | **−.317**[b] | **.255**[a] | .157 | 1 | .167 | −.028 | .097 | **.367**[a+] | .054 |
| Disease duration | .163 | .103 | .216 | .102 | .225 | .167 | 1 | .035 | −.092 | **.375**[a+] | **−.346**[a] |
| MADS | −.139 | .015 | −.021 | .212 | .059 | −.028 | .035 | 1 | .044 | .283[+] | −.152 |
| UPDRS3 | −.039 | −.230 | −.121 | −.237 | −.175 | .097 | −.092 | .044 | 1 | **.337**[a+] | **−.294**[a] |
| HYS | .101[+] | .018[+] | .115[+] | .000[+] | .086[+] | **.367**[a+] | **.375**[a+] | .283[+] | **.337**[a+] | 1[+] | **−.357**[a+] |
| ADL | .040 | .177 | .034 | −.018 | .154 | .054 | **−.346**[a] | −.152 | **−.294**[a] | **−.357**[a+] | 1 |

All correlations were calculated by Pearson's correlation except for those marked by [+] label where Kendall's tau correlation were applied.
Abbreviations: ACE: Addenbrooke's Cognitive Examination; ADL: Activities of Daily Living; FAB: Frontal Assessment Battery; HYS: modified Hoehn & Yahr Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MDRS: Mattis Dementia Rating Scale; MMSE: Mini Mental State Examination; UPDRS3: Unified Parkinson's Disease Rating Scale part 3 −motor examination. VLOM: verbal fluency + language/orientation + memory.
Bold values significance levels are indicated by labels "a" and "b".
[a] Correlation is significant at the $p < 0.05$ level.
[b] Correlation is significant at the $p < 0.01$ level.

duration did not correlate with the results of dementia rating scales.

In ROC curve analysis, the results of ACE, FAB and MDRS tests were tested against presence or absence of the clinical diagnosis of PDD to obtain optimal cut-off scores, specificity and sensitivity values.

The area under the ROC curve of Addenbrooke's Cognitive Examination was .883 [95% confidence interval (CI): .794–.976]; whereas, the best cut-off score identify PDD was 80 points (sensitivity = 74.0%, specificity = 78.1%, positive predictive value = 67.42, negative predictive value = 83.42).

For Frontal Assessment Battery the area under the ROC curve was .779 [95% CI: .641–.904] and the most optimal cut-off score assess PDD was 12 points (sensitivity = 66.3%, specificity = 72.3%, positive predictive value = 50.0, and negative predictive value = 79.9).

Mattis Dementia Rating Scale showed the best specificity and sensitivity to detect PDD in our study (area under ROC curve: .925, 95% CI: .847–1.000, sensitivity = 89.8%, specificity = 98.3%, positive predictive value = 96.4, and negative predictive value = 93.2) using the cut-off score of 125 points.

For MMSE, the area under the curve was .867 [95% CI: .820–.994]. Best cut-off value for MMSE was 26 points with the sensitivity of 79.9% and specificity of 74.0%).

## 4. Discussion

Screening for dementia in Parkinson's disease is an important clinical necessity for establishing diagnosis and initiating proper treatment. To reliably differentiate normal cognitive abilities from dementia one need an easily obtainable, reproducible and validated test battery with high specificity and sensitivity. However in Hungary only MMSE was previously validated for screening dementia in PD patients. Because MMSE does not measure the executive functions and has a ceiling effect [13], it is generally considered unsuitable for reliable PDD identification [13].

Former studies demonstrated controversial data about the usability and validity of Addenbrooke's Cognitive Examination in detecting cognitive impairment or dementia in PD [15,28]. Most studies agreed that ACE was superior and a more reliable tool than MMSE in detecting PDD. Because ACE was specially designed for detecting Alzheimer's disease, some domains specific for cognitive impairment in PD theoretically may remain unnoticed by the sole use of ACE. Although some studies demonstrated that ACE has a good correlation with the results of other PD-specific neuropsychological tools (e.g. Scales for Outcomes of Parkinson's disease − Cognition, SCOPA-PD) [15] and recommended ACE as a screening tool for PDD [29]; these studies did not implement the diagnostic criteria for PDD during the validation process [6]. Our cut-off score of ACE for screening PDD (80), however, was lower than that of international versions (83) [15]. This difference might be also due to the fact that we excluded all the patients having depression and applied different diagnostic criteria of PDD as reference.

Kulisevsky and coworkers recommended the estimation of discriminative properties of Frontal Assessment Battery in PDD [4]. In our study, however, the sensitivity and specificity of FAB did not achieve those of MMSE. Therefore, FAB as a sole screening tool for PDD might be insufficient in contradiction to the viewpoint of Robben et al. [29].

Although several European DBS centers routinely apply MDRS for screening PDD (personal information) and previous studies evaluated its creditability [15,19,20], a recently published viewpoint article on behalf of the Parkinson Study Group Cognitive/Psychiatric Working Group [13,30] recommended the application of Montreal Cognitive Assessment (MoCA) as a screening tool for PDD in trials. This recommendation left MDRS out of consideration because its administration time exceeds 15 min.

Based on our results, the MDRS demonstrated the highest sensitivity and specificity among the examined test batteries to detect PDD established by the recent clinical criteria [6]. Our cut-off score and discriminative power of MDRS (125) was nearly equal with the cut-off value of MDRS (123) in Spanish PD patients [19], but considerable less than that of French PD population (130) [20].

There is probably not a single tool capable of satisfying the different needs of different movement disorder clinics for screening PDD in the routine practice. Although the applied screening instruments might differ from center to center within a country, determination of the most specific and sensitive test for the given population remains to be an important task. Based on the validation, one might select the most optimal screening battery by the best clinimetric data. Our results demonstrated that the specificity and sensitivity of MDRS was better than those of ACE, FAB and MMSE in Hungary. The inconstancy among the previously published neuropsychological studies evaluating PDD might originate from different population characteristics, the discrepancies between the baseline clinical and demographic attributes, and more importantly the sample size. However, further studies with larger sample size and more uniform criteria for participation are

required to determine the most suitable screening instrument for cognitive impairment in PD.

## Conflict of interest

None declared.

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