Cognitive profiling of Parkinson disease patients with mild cognitive impairment and dementia

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A B S T R A C T

Background: Prevalence of mild cognitive impairment (MCI) and dementia in Parkinson disease (PD) is variable because different classification criteria are applied and there is lack of consensus about neuropsychological tests and cut-off used for cognitive profiling. Given the important therapeutic consequences for patient management, we aimed at identifying suitable diagnostic cognitive tests and respective screening cut-off values for MCI and dementia in PD (PDD).
Methods: We evaluated 105 PD patients using an extensive neuropsychological battery categorized as PD without cognitive impairment (PD-CNT) (35%), PD-MCI (47%) and PDD (18%) based on established criteria and calculated Receiver Operating Characteristic (ROC) curves.
Results: We found different sensitivity and specificity among neuropsychological tests in detecting PD-MCI and PDD. In particular performance in attention/set shifting, verbal memory and language abilities, discriminated both PD-MCI and PDD from PD-CNT. Abilities involved mainly in semantic retrieval mechanisms discriminated PD-CNT from PD-MCI but also PD-MCI from PDD. Finally deficits in executive and visual-spatial abilities were only affected in PDD.
Conclusion: Our data point to an independent and different load of each test in defining different PD cognitive statuses. These findings can help selection of appropriate cognitive batteries in longitudinal studies and definition of stage-specific therapeutic targets.

1. Introduction

Parkinson disease (PD) is a multidimensional progressive disorder with a number of motor and non-motor features including cognitive dysfunction [1]. Even if the risk of dementia is increased in PD compared to healthy controls [2], it is conceivable that only specific cognitive symptoms are germane to development of dementia [3]. In this regard the concept of mild cognitive impairment (MCI), initially developed to detect cognitive changes in preclinical Alzheimer disease (AD) has received increased attention also in PD [4]. MCI is characterized in PD by cognitive changes perceived by patients and familiars that are not related to the normal cognitive age-decline, and with functional daily living autonomy that excludes diagnosis of dementia [5]. PD-MCI patients have an increased risk of dementia with an annual incidence between 9% and 15% [6,7] and clinical and demographic variables (mainly age and disease duration) affecting the rate of cognitive decline [3,8]. The Movement Disorders Society task force issued specific criteria for PD-MCI diagnosis and suggested tests covering cortical and subcortical mediated functions [9]. However, there are methodological ambiguities that make identification of MCI as well as prediction of future development of dementia in individual patients a challenge and ultimately affect the frequency of MCI. For example even if the Montreal Cognitive Assessment (MoCA) is suggested as recommended scale for cognitive screening, its discriminant ability has been recently questioned [10]. Moreover differences in reported PD-MCI prevalence rates maybe associated with the use of abnormality threshold ranging from −1 to −2 standard deviations (SD) below the mean of normal population in one test in two domains or two tests in one domain [11] which increases type I and II errors [12]. Indeed, threshold values do not place patients' cognitive impairment in the continuum between normal cognition and dementia but can only be considered dichotomous criteria for exclusion/inclusion in a specific cognitive state. Rather than using coarse thresholds of standard deviation it would be more appropriate to define specific cut-off values for each test, which should

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increase sensitivity and specificity in assessing the cognitive state of the patient examined [13].

In this study, therefore, we evaluated which neuropsychological tests best discriminate different PD cognitive stages (PD-CNT vs. PD-MCI vs. PDD) and also provided, for the first time, valid cut-off values for tests to be used in prospective studies to assess progression to dementia.

2. Methods

We selected participants at the Parkinson disease Unit of the 'San Camillo' Hospital (Venice-Lido, Italy) collected from a database build up between April 2012 and April 2013. From a sample of consecutive 112 PD diagnosed according to UK Brain Bank criteria, coming for first clinical assessment, we included 105 patients who underwent in the morning "on" treatment state a complete neuropsychological assessment (7 patients could not undergo a complete clinical and neuropsychological evaluation) by trained neuropsychologist (RB, SF, PD).

We did not consider patients with atypical Parkinsonism as well as those who had clinically serious cardiovascular, metabolic and psychiatric diseases or neurosurgical procedures (including deep brain stimulation). Compared to another series we have recently published [13] this is a new independent PD cohort performing a more extensive neuropsychological battery including tests we had not previously investigated such as MoCA. We calculated Levodopa Equivalent daily Dose (LDED) and Dopamine Agonist Equivalent daily Dose (DAED) for each patient [14]. Clinical severity was graded using the Hoehn and Yahr (H&Y) and the motor Unified Parkinson Disease Rating Scale (UPDRS-III). Demographic data (age, gender and education level) and neurological details (age at onset, disease duration) were also collected.

All patients participating in the study spoke fluent Italian as first language and had a brain MRI with no otherwise clinically relevant structural alterations. The ethics committee of the IRCCS San Camillo, Venice (Italy) approved study. All participants signed an informed consent explaining the nature of the study. The research was completed in accordance with the Helsinki Declaration.

3. Neuropsychological examination

Our neuropsychological protocol included Mini Mental State Examination (MMSE) and MoCA to assess general cognitive functions. Attention/working memory domain was tested by the Trail Making Test [15], Digit Span Forward [16], Digit Ordering Test version B (DOT-B) [17] and Corsi's test [16]. Executive functions were evaluated by phonological fluency task to assess response generation and set-maintenance of task instruction [18] and the Stroop Color/Word test [19]. Memory was assessed by the Rey–Osterrieth Complex Figure test (ROCF) delayed recall [20], word paired associated task and prose memory tests [21]. Language was tested by the category fluency task, WAIS-IV similarities test to measure verbal comprehension (abstract verbal reasoning) [18] and Novelli's naming task [18]. Visuo-spatial and visuo-perceptive functions were assessed by the ROCF copy [19], Visual Object and Space Perception Battery (VOSP) uncompleted recognition letter task [22] and Free-drawn Clock Drawing Test (CDT) [23]. We used the Beck Depression scale (BDI-II) [24] to assess presence of depression (range score 0–63) and measure severity of depressive symptoms. We also administered the 8-item version of Parkinson's disease quality of life (PDQ-8). Standardized, published normative Italian datasets were used as comparative references to determine impairments.

4. Cognitive categorization

Based on cognitive profile, patients were categorized in 3 subgroups: PD-CNT, PD-MCI and PDD. Dementia was diagnosed according to the Movement Disorder Society task force recommendation criteria [25] based on neuropsychological tests, functional autonomy as well as clinical interview. PD-MCI was diagnosed based on MDS Task Force recommendations for PD-MCI Level 2 criteria (comprehensive assessment) and required 1) presence of subjective cognitive complaints from patients or caregivers, 2) abnormal functional independence assessed by ADL/IADL during a clinical interview and 3) impaired cognitive performance on at least 2 tests for each domain or 1 test in two domains. Altered performance of each neuropsychological test was defined as a score that was at least ≥ -1.5 SD the age-adjusted mean from normative samples. MCI patients were diagnosed based on performance in the five cognitive domains. Individuals with z-score at each cognitive test < -1.5 SD of normative sample mean or with only one abnormal test were considered cognitively intact. To this end, z-scores were obtained using relative published Italian normative data adjusted for age and education. We used a -1.5 SD threshold to minimize the inclusion of cognitively intact patients [12]. For individual neuropsychological test administered to evaluate each single domain see Supplementary e-Table I.

5. Statistical analyses

Clinical and demographic variables were analysed using Pearson Chi-square test and One-way ANOVA followed by Dunnet post hoc test ($p < 0.05$). For cognitive data, we run General Linear Model (GLM) considering age and education adjusted test scores, including in the model as covariates clinical variables that were significantly different among subgroups. Bonferroni correction was applied with a p value <0.003. Receiver Operating Characteristic (ROC) curves with Area Under the Curve (AUC) (95% CI) were also computed. A corrected $p < 0.005$ was used as inclusion criteria in the ROC analysis. AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and percentage of correctly diagnosed were calculated for each test. We defined the optimal cut-off point as the value obtained by the intersection of sensitivity and specificity scores of each test. The screening cut-off point was defined as the value achieving $>80\%$ sensitivity and NPV. The diagnostic cut-off point was defined as the value achieving $>80\%$ specificity and PPV. All statistics were performed using SPSS version 20 (IBM SPSS, Chicago, IL).

6. Results

In our series of 105 PD patients (32 males and 73 females) [mean age 64.6(SD 10.5), education 11.1(SD 4.1)] there were 37 PD-CNT (35%), 49 PD-MCI (47%) and 19 PDD (18%).

Between-group analysis (ANOVA) showed significant differences among PD subgroups in age ($p < 0.0001$), ADL ($p < 0.0001$), IADL ($p < 0.0001$), age of onset ($p < 0.003$), motor severity [H&Y and UPDRS-III ($p < 0.0001$)], dopaminergic medication dose ($p < 0.005$), quality of life ($p < 0.0001$) and depression mean scores ($p < 0.02$). Post-hoc comparisons showed a significant linear trend in differences of mean age, functional and instrumental autonomy, motor severity and age of onset between PD subgroups (PD-CNT $<$ PD-MCI $<$ PDD). Moreover, PDD had the lowest mean medication dose, the worst quality of life and the highest mean depression score. There were no gender differences between cognitive subgroups at chi square analysis (PD-CNT vs. PD-MCI vs. PDD). However, there was a positive correlation between female