What predicts cognitive decline in de novo Parkinson's disease?

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Abstract

Subtle cognitive impairment can be detected in early Parkinson's disease (PD). In a consecutive series of de novo, drug-naive PD patients, we applied stepwise regression analysis to assess which clinical, neuropsychological, and functional neuroimaging (dopamine transporter [DAT] and perfusion single photon emission computed tomography [SPECT]) characteristics at baseline was predictive of cognitive decline during an average follow-up time of about 4 years. Decline both in executive ($R^2 = 0.54$; $p = 0.0001$) and visuospatial ($R^2 = 0.56$; $p = 0.0001$) functions was predicted by the couple of Unified Parkinson's Disease Rating Scale (UPDRS)-III score and caudate dopamine transporter (DAT) uptake in the less affected hemisphere (LAH). Verbal memory and language decline was predicted instead by caudate DAT uptake and brain perfusion in a posterior parieto-temporal area of the less affected hemisphere ($R^2 = 0.42$; $p = 0.0005$). No significant effect was shown for age, baseline neuropsychological scores, and levodopa equivalent dose at follow-up. The combined use of clinical structured examination and brain functional assessment by means of dual single photon emission computed tomography imaging appears as a powerful approach to predict cognitive decline in de novo PD patients.
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1. Introduction

Cognitive impairment is increasingly recognized in Parkinson's disease (PD) since the early stages, when a subtle dysexecutive syndrome can be found in the majority of patients, mainly consisting of deficit in planning and cognitive flexibility (Kehagia et al., 2010). Moreover, deficit in learning, memory, and visuospatial function variably overlaps the dysexecutive syndrome and has contributed to the emerging concept of mild cognitive impairment (MCI) in PD (Caviness et al., 2007) as a condition possibly preceding

PD dementia (PDD), similarly to the conceptual construct adopted for Alzheimer's disease (AD) (Aarsland et al., 2010). MCI in PD has been associated to subsequent decline in motor impairment, quality of life, and disability (Post et al., 2011) and has been shown to predict increased mortality risk (Lo et al., 2009). Thus, cognitive impairment could be an independent aspect of PD with a relevant role in determining functional outcome before the onset of PDD.

Therefore, knowing the cognitive status and its evolution when PD is diagnosed for the first time could have a relevant prognostic meaning. Whereas advanced age, severity of motor disease, postural instability, and an akinetic-rigid syndrome are the main risk factors for the early onset of PDD (Aarsland et al., 2008), little is known on which signs or symptoms at disease onset are associated with mild but detectable, subsequent cognitive decline.

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Few functional imaging studies have addressed this issue. An ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) study has identified a Parkinson's disease-related metabolic cognitive pattern (PDCP) (Huang et al., 2008), significantly more expressed with the worsening of the disease (Huang et al., 2007b). This PDCP mainly includes precuneus, inferior parietal lobule, angular and lingual gyri, and superior and middle frontal gyri and significantly correlates with tests exploring executive functions, visuoperceptive abilities, memory, and language (Huang et al., 2007a). Hypometabolic PDCP expression has already been detected in the "presymptomatic" (i.e., ipsilateral) hemisphere of PD patients with hemi-parkinsonism (Tang and Eidelberg, 2010). In a single photon emission computed tomography (SPECT) study, at baseline perfusion levels in right medial frontal, left parietal, and left lenticular nucleus together with semantic and alternating word fluency, and Stroop interference index have been found to significantly predict cognitive decline after a 3-year follow-up in a group of drug-naive PD patients (Dujardin et al., 2004). Early acethylcholinesterase deficit has been shown in de novo PD patients by means of [11C]MP4A PET (Bohnen et al., 2003) but its role in subsequent decline needs to be further explored.

Nigrostriatal degeneration, mainly at caudate level, and the consequent dopamine striato-frontal depletion syndrome has been repeatedly involved in cognitive impairment of PD (Cropley et al., 2006; Emre, 2003; Jokinen et al., 2009; Nobili et al., 2010; Rinne et al., 2000). Correlation between nigro-caudate dopaminergic impairment and tests exploring executive functions has been reported by means of [123I]β-CIT or FP-CIT (N-ω-fluoro-propyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane) SPECT (Duchesne et al., 2002; Müller et al., 2000; Nobili et al., 2010) and PET radiopharmaceuticals, including presynaptic imaging with ^{18}F-DOPA (dihydroxyphenylalanine) (Rinne et al., 2000) and [11C]nomifensine (Marié et al., 1999), and postsynaptic D2 imaging with [11C]raclopride (Sawamoto et al., 2008). However, despite this evidence of a tight relationship between nigro-caudate dysfunction and executive function impairment, the role of nigrostriatal deafferentation in predicting subsequent cognitive decline at disease onset has not yet been investigated.

In this study we collected baseline demographic, clinical, neuropsychological, and brain functional parameters, including dopamine transporter (DAT) activity and brain perfusion levels by means of SPECT, in a consecutive series of drug-naive patients with de novo PD. The patients were then treated with dopaminergic agents and a cognitive assessment was repeated after an average time of about 4 years. We were aimed at analyzing which parameters collected at baseline were significantly associated with cognitive decline 4 years later.

2. Methods

2.1. Patients

Thirty consecutive patients with de novo PD, never treated with dopaminergic stimulation (drug-naive), were enrolled. The diagnosis of PD followed current criteria (Gelb et al., 1999). The patients underwent brain magnetic resonance imaging (MRI), or computed tomography (CT) in the case MRI was unfeasible, to rule out other brain diseases. Patients with brain infarcts on MRI/computed tomography or with a history of stroke or transient ischemic attacks were excluded, whereas the presence of small white matter hyperintensities on MRI was not an exclusion criterion. Dementia was excluded by means of clinical interview and questionnaires for activities of daily living (ADL) (Katz et al., 1970) and instrumental ADL (Lawton and Brody, 1969). The Clinical Dementia Rating (CDR) scale was 0 in 26 patients and 0.5 in 4 patients. The Mini Mental State Examination (MMSE) was used as a measure of global cognitive function. The 15-item geriatric depression scale was administered to assess depression. Motor severity of disease was assessed by the Unified Parkinson's Disease Rating Scale, motor section (i.e., Unified Parkinson's Disease Rating Scale [UPDRS]-III).

Patients underwent a neuropsychological test battery, including: (1) 6-trial selective reminding test (SRT) for verbal episodic memory (immediate and delayed recall); (2) categorical and phonological verbal fluency; (3) figure copying of the mental deterioration battery (simple copy and copy with guiding landmarks) to assess visuoconstructional abilities; (4) Raven's PM (Progressive Matrices) 47, investigating logical reasoning and visuospatial functions; (5) visual search test to study sustained attention and ideomotor speed; (6) Trailmaking test (A and B, with computation of B-A score) to explore visuomotor abilities, divided attention, and attention shifting; (7) Stroop color-word test for cognitive flexibility and executive functions; (8) symbol digit test to assess executive functions and working memory; (9) Corsi's block design to investigate spatial memory; (10) digit span (forward) assessing auditory memory span; and (11) Clock Completion test as a mixed measure of executive functions, visuospatial abilities, and memory. References for tests and normative values are listed in a previous report (Nobili et al., 2010).

The 30 patients underwent DAT-SPECT, while in 4 of them brain perfusion SPECT was not feasible because of logistic reasons. DAT-SPECT scans were visually reported by nuclear medicine physicians in our group (SM and GS). Moreover, semiquantitative uptake values (normalized on background activity) in each patient were compared with those from a reference control group ranging in age between 40 and 90, embedded within the BasGan V2 software (freely available on the Italian Association of Nuclear Medicine [AIMN] web site: www.aimn.it/struttura_index.php.), taking age into account (Guerra et al., 2009). DAT-SPECT scan was impaired in all patients by both visual and semiquantitative evaluation.

All of them started treatment with dopamine agonists and/or L-DOPA, according to clinical judgment of the same neurologist and were followed-up with clinical and neuro-