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Cognitive and behavioural assessment of parkinsonian syndromes at onset: a longitudinal study

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Cognitive and behavioural assessment of parkinsonian syndromes at onset: a longitudinal study.

1. Introduction

Parkinsonism, characterized by tremor, rigidity, bradykinesia and postural instability, is a cardinal feature of a wide group of neurodegenerative disorders and a common finding in neurological outpatient clinics. The incidence ranges from an estimated 0.5/1000 person-years for patients aged between 55 and 65 years to 10.6/1000 person-year for those aged above 85 years [1]. Early in the course of the disease, establishing a correct diagnosis can be challenging due to overlap in the clinical presentation between the various forms of parkinsonism (Table 1). However, being able to differentiate between Parkinson's disease (PD) and Parkinsonian syndrome (PS) is highly relevant. The majority of patients with parkinsonism have idiopathic Parkinson's disease (PD), a neurodegenerative syndrome clinically characterized by resting tremor, rigidity, bradykinesia, asymmetric onset and sustained response to levodopa or dopamine agonist [2]. The prevalence rates of PD ranged from 108 to 257 per 100,000 persons, and the annual incidence rates ranged from 11 to 19 per 100,000 persons [3].

The differential diagnosis with PD is broad and includes, among others, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy bodies (DLB) and secondary causes of parkinsonism (Table 2) [4].

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterized clinically by various combinations of autonomic, cerebellar, parkinsonian, and pyramidal features [5]. The prevalence rate is below 5 and the incidence rate is below 1 in 100,000 [6].

Lewy body dementia (DLB) is the second most common cause of neurodegenerative dementia after Alzheimer Disease (AD), with a prevalence of 19%. It is clinically diagnosed by a progressive cognitive decline sufficient to interfere with normal social or occupational function, fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations and spontaneous motor features of parkinsonism [7].

There is considerable overlap between DLB and Parkinson's disease with dementia (PDD). The diagnosis of PDD designates dementia that develops within the context of established PD, whereas a diagnosis of DLB is appropriate when the diagnosis of dementia precedes or coincides within 1 year of the development of motor symptoms [8].

Progressive supranuclear palsy (PSP) is characterized by either vertical supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of disease

onset [9]. Its incidence increases with age, from 1.7 cases per 100,000 per year at 50–59 years to 14.7 per 100,000 per year at 80–99 years [6].

Corticobasal degeneration (CBD), a distinctive pathological condition, is clinically characterized by a slow onset and progressive asymmetric cortical and extrapyramidal dysfunction described as akinetic rigid syndrome, levodopa-resistant, associated with prominent apraxia, cortical sensory loss, focal reflex myoclonus, dystonia, alien limb phenomenon without an early dementia [10]. CBD may have several different clinical presentations aside from the Corticobasal syndrome, including frontotemporal dementia, primary progressive aphasia, progressive speech and oral apraxia, and dementia with behavioral changes, apraxia, and parkinsonism. The relative frequencies of these manifestations is unknown [11].

Despite advances in our understanding of degenerative parkinsonian disorders, currently there are no reliable biomarkers to separate them, and a definitive diagnosis can only be made on neuropathological examination [12].

Efforts to study large de-novo cohorts with longitudinal follow-up are ongoing worldwide [13-18] in order to obtain in vivo results of establishing a correct diagnosis early in the course of the disease.

Distinguishing these disorders clinically, particularly in the early stages, poses immense challenges, even to movement disorder specialists [12, 19-20]. The diagnostic accuracy of the initial diagnosis varies greatly in PD, with accuracies of 76 % in the hands of a general neurologist to up to 90 % by movement disorder specialists [21, 22]. Furthermore, a recent study reported that the accuracy for a clinical diagnosis of PD is 26% in untreated or not clearly responsive subjects, 53% accuracy in early PD responsive to medication, and 85% diagnostic accuracy of longer duration, medication-responsive PD [23].

The diagnostic accuracy is lower for patients with a form of AP, e.g., 41–88 % in PSP; [24] and 50–66 % in MSA [5].

Cognitive impairment is one of the non motor features widely described in parkinsonian syndrome, it has been related to the motor characteristics of the parkinsonian syndrome, associated with neuropsychiatric dysfunction and the characteristic sleep and autonomic features [36-37].

It has been shown to be highly prevalent at all disease stages and to contribute significantly to disability [11].

Several studies aimed to characterize the cognitive profiles of each parkinsonian disorders [36], others [reviewed in 12] aimed to define the contribution of cognitive testing to differentiate parkinsonian disorders at onset, reporting conflicting results. This conflicting results could be

related both to study design and to the overlap and to the heterogeneity of the clinical picture of parkinsonian disorders [12].

Aim of this study is:

1) to evaluate longitudinally the cognitive and behavioral characteristics of patients with a parkinsonian syndrome at onset;

2) to describe the cognitive and behavioral characteristics of each parkinsonian syndrome;

3) to define in PD patients at onset the presence of MCI or Parkinson disease dementia;

4) to correlate the cognitive and behavioral characteristics with the features of the parkinsonian syndrome and with the associated sleep and autonomic features.

2. Patients and Method

2.1 Inclusion criteria

We consecutively recruited patients, aged between 18 and 90 years, evaluated at the Movement Disorders Centre of our Department for a neurodegenerative disease starting with parkinsonian features (tremor, bradykinesia, rigidity, postural instability) and disease duration up to 3 years.

2.2 Exclusion criteria

Patients affected by secondary causes of parkinsonism (Table 2) were excluded.

2.3 Diagnostic procedures

Each patient performed the follow evaluations:

- clinical history,

- neurological examination (including assessment of motor impairment by means of UPDRS part III [24]),

- neuroimaging studies (brain MRI and DAT Scan),

- quantification of motor response to standard oral levodopa test (based on simultaneous serial measurements of plasma levodopa concentrations, finger-tapping motor effects, and dyskinesia ratings), levodopa equivalent dose (LED) was calculated for each patients [25],

- evaluation of autonomic control of the cardiovascular system through cardiovascular reflex tests (Tilt test, Valsalva's manoeuvre, Handgrip test, Deep breathing test) [26] and evaluation of autonomic dysfunction through the questionnaire SCOPA-AUT: Scales for Outcomes in Parkinson's Disease – Autonomic [27,28],

- assessment of sleep disturbance by means of a whole night video-polysomnographic

(VPSG) study and through questionnaires (PDSS: Parkinson's disease sleep scale 1 [29]; RBD: REM sleep behaviour disorder questionnaire [30], BQS: Bologna questionnaire on sleepiness-related symptoms [31], ESS: Epworth sleepiness scale [32], RLS: Restless Legs Syndrome criteria and rating scale [33], PDQ-39: 39-item Parkinson's disease questionnaire [34],

- cognitive and behavioural assessment (see below).

Neuroimaging studies were performed at baseline.

The other procedures were performed at baseline (T0) and after 16 months (T1).

Diagnosis was carried out at T1 according with international diagnostic criteria for the diagnosis of PD [2], MSA [5], DLB [7], PSP [9] and CBD [10].

Patients not fulfilling international diagnostic criteria were diagnosed as parkinsonian syndrome not otherwise specified (PS).

All clinical data useful for diagnosis of PD, MSA, PSP, LBD, CBD were tabulated with full details in a database developed ad hoc for this study.

2.4   Cognitive and behavioural assessment

We built up a neuropsychological assessment in order to recognize the initial cognitive and behavioral features of the different parkinsonian syndrome according to the Movement Disorder Society Task Force criteria and revision of literature [12-35].

Neuropsychological evaluation is described in Table 3.

All test results were corrected for age, sex and education according to Italian standardizations (Table 3).

2.5   Definition of cognitive impairment

Definition of cognitive deficit: one or more test impaired according to cut-off score corrected for age, sex and education according to Italian standardization.

If at least one test was impaired according to cut-off score of corrected score according to Italian standardization the patient had cognitive impairment.

Impairment in cognitive domain was defined if at least one test was impaired in that domain (for the relation cognitive test to cognitive domain, see Table 3).

Progression of cognitive impairment was defined if one more test was impaired at T1.

Improvement of cognitive impairment was defined if one test less was impaired at T1.

2.5.1 Inclusion criteria for PD-Mild Cognitive Impairment

A further analysis was conducted in patient with PD. Patients with a diagnosis of Parkinson's disease [20] and gradual decline in cognitive ability reported by either the patient or informant, or observed by the clinician; cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities according to Specific guidelines for PD-MCI level II categories (Table 11) [38]; cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present.

2.5.2 Exclusion criteria for PD-MCI

Diagnosis of PD dementia based on MDS Task Force proposed criteria [18], other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma), other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing.

2.6 Statistical analysis

Descriptive analysis of demographic and neuropsychological data has been reported.

3. Results

3.1 Description of the sample

We recruited 91 patients.

6 patients dropped-out after the baseline evaluation (Table 4. Demographic data of dropped-out patients).

55 of 91 patients completed the second evaluation (T1).

According to international diagnostic criteria 39 patients were diagnosed as PD, 2 as CBS, 1 as MSA, 2 as PSP, 11 as PS not otherwise specified.

55/55 patients performed the brief neuropsychological evaluation both at T0 and T1.

20/55 (14 PD, 5 PS, 1 CBS) patients performed the comprehensive neuropsychological evaluation both at T0 and at T1.

Demographic and clinical data are shown as mean and standard deviation in Table 5.

The means and standard deviations results of the cognitive battery administered to patients are presented in Table 6 and 7.

At T0, 29 (23 PD and 6 PS) patients did not present cognitive impairment.

13 (7 PD, 4 PS, 1 CBS, 1 MSA) patients were impaired in one domain:

- 12 (6 PD, 4 PS, 1 CBS, 1 MSA) in attention or executive function;
- 1 PD in fluency.

In one case (MSA) the impairment in one cognitive domain was related to an impairment in 3 test (assessing the same cognitive domain), in the other cases only one test per domain was impaired.

6 PD patient were impaired in two domains:

- 2 were impaired in executive function and verbal memory;
- 1 in executive function and attention;
- 2 in attention and fluency;
- 1 in verbal memory and fluency;

In two cases (PD) the impairment in one cognitive domain was related to an impairment in 2 test (assessing the same cognitive domain), in the other cases only one test per domain was impaired.

4 patients were impaired in three cognitive domains:

- 2 (1 PSP, 1 PD) attention and executive function and fluency;
- 1 PD was impaired in attention and fluency and verbal memory;
- 1 CBS was impaired in attention and fluency and praxis.

In two cases (PD, PSP) the impairment in one cognitive domain was related to an impairment in 2 test (assessing the same cognitive domain), in the other cases only one test per domain was impaired.

2 patients (1 PD, 1 PS) were impaired in four cognitive domains:

- 1 PD was impaired in attention and executive function and verbal memory and fluency;
- 1 PS was impaired in attention and executive function and verbal memory and visuospatial function.

In both cases two test were impaired at least for one of the impaired domains.

One patient (PSP) showed a global cognitive impairment.

3.2 Longitudinal evaluation of cognitive characteristics of patients with a parkinsonian syndrome at onset – brief neuropsychological evaluation

22/55 patients (17 PD and 5 PS) did not present cognitive impairment both at T0 and at T1.

18/55 patients presented a progression of cognitive impairment (at least one more cognitive domain impaired at T1):

- 6/18 (5 PD and 1 PS) patients were not impaired a T0 and presented a progression of cognitive impairment at T1:

- 5 PD patients presented an impairment in attention or executive function;
- the PS patient presented an impairment in verbal memory.

- 12/18 patients (6 PD , 2 PSP, 1 CBS, 3 PS) presented a progression of cognitive impairment:

- 2 PS were impaired in attention and executive function;
- 1 PD was impaired in attention and executive function and praxis;
- 2 PD were impaired in attention and executive function and verbal memory;
- 1 PSP was impaired in attention and executive function and verbal memory and fluency;
- 1 PD and 1 CBS in attention and executive function and praxis and fluency;
- 4/18 (2 PD, 1 PSP, 1 PS) patients presented a progressive global cognitive impairment.

Figure 1 shows the progression of cognitive impairment from T0 to T1.

8/55 (6 PD and 2 PS) patients presented an improvement of cognitive deficits at T1.

7/55 patients (5 PD, 1 MSA, 1 CBS) remained stable at T1.

Figure 2,3 and Table 8 show the percentage of patients failing each neuropsychological test in progressive and not progressive patients.

26 out of 55 patients (47%) failed at least one test in the neuropsychological test at T0.

Most of the patients failed to perform correctly STROOP and SVAT, WF and BARR in both groups of patients. The frequency of impairment was less than 15% on the remaining test.

In the comprehensive battery, some test (RFC, BS, CS, TMT, MP, Token) were performed correctly in the whole group/by all the patients. (Table 8 and 9. Impaired test and domain).

The domains failed by most of the patients were attention (n =45), executive function (n =36), verbal memory (n =21) and fluency (n=21) equally affected; almost equally affected (praxis, visuospatial memory and cortical sensibilities). Comprehension was spared.

Considering the 18 patients with a progression of cognitive impairment only 5 of them at T0 and 7 of them at T1 presented a deficit in test or battery evaluating global cognitive impairment:

At T0

- 2 PS-PSP;
- 3 PD (patient 28: FR BBDM, attention and executive function and verbal memory; patient 22: FR BBDM, progressive global cognitive impairment, patient 10: MMSE, progressive global cognitive impairment).

At T1

- 2 PS-PSP;
- 1 CBS;

- 3 PD (patient 59: FR BBDM, attention and executive function and verbal memory; patient 25: FR BBDM, attention and executive function and praxis and fluency; patient 10: MMSE progressive global cognitive impairment);
- 1 PS (patient 51 presented a significant progression LTVM, SVAT, WF, BARR, STROOP).

The other PD progressive patient (patient 5, impaired in attention and executive function and praxis) did not present impairment in FR BBDM and MMSE.

3.3 *Longitudinal evaluation of cognitive characteristics of patients with a parkinsonian syndrome at onset – comprehensive neuropsychological evaluation*

20 (14 PD, 5 PS, 1 CBS) patients performed the comprehensive evaluation.
Of these patients:

- 1 PD did not present cognitive impairment both at T0 and T1;
- 2 (1 PD, 1 PS) patients presented an improvement of cognitive impairment ;
- 10 (7 PD, 1 CBS, 2 PS) patients presented a stability of cognitive impairment;

7/20 (5 PD, 2 PS) patients presented a progression of cognitive impairment (at least one more domain impaired):

- 4/ 7 patients (3 PD and 1 PS) were not impaired at T0 and presented a progression of cognitive impairment at T1. These patients presented an impairment in attention or executive function.
- 3/7 (2 PD, 1 PS) presented a progression of cognitive impairment:

- 1 PS was impaired both in attention and executive function;
- 1 PD was impaired in attention and executive function and verbal memory;
- 1 PD was impaired in executive function and verbal memory and visuospatial function.

Discussion

Patients with parkinsonian syndrome and progressive cognitive impairment showed mainly an impairment in attention and executive function, both at onset and during the progression of the disease.

Comparing the neuropsychological evaluation performed at T0 with the longitudinal evaluation at 16 months, we observed that 29% of patients presented a progression of cognitive impairment, 15% showed an improvement in cognitive evaluation, 13% of patients were stable and 41% of patients did not show impairment both at T0 and T1.

According to these findings, the evaluation of cognitive function at onset in patients with parkinsonian syndromes is mandatory to document early cognitive decline and its frequency, to

identify motor and non motor correlates of impaired baseline cognition and to understand phenotypic heterogeneity. Furthermore neuropsychological evaluation at follow-up is necessary to detect longitudinal changes of the cognitive impairment, including the pattern of impairment, its eventual progression, especially in patients with a suspicion of dementia or typical syndrome. In atypical presentation of parkinsonian syndrome neuropsychological evaluation is even more essential for the clinician that should be able to build a clinical profile in conjunction to the other features of parkinsonian syndrome [90].

Furthermore, our study confirm the need of a complete neuropsychological evaluation as test assessing global function as MMSE could be not enough sensitive to disclose and to describe different pattern of impairment. On the contrary, the detection of normal MMSE could be not enough specific, either at follow-up, to exclude cognitive dysfunction.

Although a detailed neuropsychological evaluation could be important to define the characteristic of cognitive impairment, the majority of the test in the comprehensive battery were always normal. Furthermore "a too detailed battery" could be overloaded for several reason: some of our patients showed just a test impaired despite several test assessing the same cognitive domain, probably overestimating the cognitive impairment.

The aim to identify bedside cognitive tests, analogous to clinical signs, that may assist clinicians in differentiating parkinsonian disorders has to be discussed considering that cognitive tests never purely assess a single cognitive domain and that, on the contrary, cognitive domains are similarly multifaceted, so that they cannot be fully assessed by a single test (Table 3). Furthermore, it has to be taken into account the confounding factors of motor impairment in test assessing cognitive function by means of a motor act (for example TMT and BARR).

It means also that the use of a well structured battery, discussing the utility of test that need motor act, is one of the most important issue in recognizing cognitive impairment in parkinsonian syndrome.

3.4 Description of the cognitive characteristics of each syndrome (Table 6 and 7)

At T0, the different disease group were characterized by a different pattern of impairment.

In particular the MSA patient showed a subtle remittent impairment of attention and executive function, reporting impaired performance according to cut-off scores only in subtest exploring attentive function (IVM, BARR, STROOP) and on the contrary, results to the other test (STVM LTVM IVM SVAT WF) similar to the group of not impaired patients.

PSP showed a global cognitive impairment, reporting the lowest score in the majority of the performances, both in respect to the other subgroups of impaired patients and cut-off scores. PSP patients did not achieve scores similar to the group of not impaired patients.

PD and PS patients presented a heterogeneous pattern of cognitive impairment, reporting intermediate scores of cognitive performance in respect to the other groups of patients, and in both subgroups of patients no similar progression of cognitive impairment was been observed .

In both subgroups of patients attention and executive function were the domains failed by most of the patients. In respect to cut-off scores, PD were never impaired while PS were impaired in test assessing attentive function (BARR and STROOP).

We observed two DCB patients. Both patients were impaired in executive function and praxis, 1 of the two patients within a global cognitive impairment. In respect to the other groups, CBD presented lower CD scores, impaired considering cut-off scores. Results to the other test (STVM LTVM IVM SVAT WF) were similar to the group of not impaired patients.

Considering test assessing global cognitive impairment, the analysis revealed that 2/2 (100%) of PSP patients were impaired and 1/2 CBD (50%) and 4/ 39 PD (10 % of PD patients).

The other subgroup of patients did not present a global cognitive impairment.

Discussion

Previous studies identified numerous cognitive tests able to differentiate parkinsonian disorders with statistical significant difference, but without a real clinical significance [36, 38-39]. According to our results, the contribution of each neuropsychological test to diagnosis at onset is not very useful. Furthermore, as discussed in the previous section, this evaluation should be made at onset and at follow-up. In addition, a standardized well structured battery of widely available, cost-effective, and easy-to-administer tests should be used in order to ensure translatability into clinical practice. Although the role of each cognitive testing may be of limited benefit in

differential diagnosis, it is still important to document neuropsychological deficits and profile for several very practical purposes.

Our study confirm previous report [36] discussing the characteristic cognitive profiles of each parkinsonian disorders. Furthermore our data suggest a common pattern of impairment (deficit in BARR T, WF, STROOP T and E; Frontotemporal Dementia like) across the different parkinsonian syndrome with an analogous common pattern of normality (sparing of long term memory).

In this optic, as with other clinical signs, cognitive features reflect the topographic distribution of pathology, regardless of the pathology type [39-40]. Thus, cognitive features arguably predict clinical syndromes rather than underlying pathologies. However, some clinical syndromes, when presenting in their classic form, are reasonably predictive of the underlying type and distribution of pathology. Characteristic cognitive features are therefore good surrogate predictive markers of underlying pathologies when applied to classic presentations. Their usefulness reduces as the presentation shifts away from the ''typical'' end of the clinical spectrum of a disease. The clinician must therefore bear in mind the potential clinical overlap of different pathological entities. Furthermore, serial cognitive testing in the clinic may avoid missing the evolution of dementia and highlight deficits of such severity as to call the patient's capacity into question, with clear implications for therapeutic and other management decisions.

3.5 Cognitive and behavioural assessment of patients with Parkinson disease at onset

We recruited 39 PD patients.

Demographic and clinical data on all included patients are shown in Table 5.

The means and standard deviations for results of the cognitive battery administered to patients are presented in Table .

At T0 22/39 PD patients did not present cognitive impairment.

At T1 27/39 patients did not present cognitive impairment.

6 PD- MCI were diagnosed at T0.

Of these patients 4 were multiple amnestic , 1 multiple non amnestic, 1 single amnestic.

At T1, 7 patients were diagnosed as PD-MCI.

Of these 7 patients 3 were diagnosed as PD-MCI at T0.

1/ 4 PD-MCI multiple amnestic patients evolved in single amnestic patients,

2/4 (patients 10 and 22) remained multiple amnestic,

The remaining 4 patients did not present cognitive impairment at T0.

All these patients presented a non amnestic impairment (3 multiple, 1 single).

The other 3 patients (multiple amnestic, multiple non amnestic, single amnestic) impaired at T0 did not present cognitive impairment at T1.

The other 11 patient at T0 and 5 patients at T1 presented different degree of cognitive impairment not accomplishing the diagnosis of PD-MCI.

Discussion

Cognitive impairment and dementia are common in Parkinson's disease (PD), with a long-term cumulative prevalence of 80% for PD dementia (PDD) [41]. According to a recent study, Mild Cognitive Impairment, appears to be common even in newly diagnosed, drug-naive PD patients [42]. Previous studies evaluated the presence of cognitive impairment at PD onset and at follow-up [43-45] but no study assessed the diagnosis of PD-MCI during the follow-up.

This study investigated the presence of MCI in a sample of 39 de novo PD patients.

The prevalence of PD-MCI at T0 and at T1 was respectively 15% and 17%, similar to the 14.8% reported by Poletti and colleagues. Previous studies reported an higher prevalence of MCI in PD patients ranging between 18 and 36%. Conversely, the evaluation of the stability of the diagnosis of MCI at follow-up in the sample of newly diagnosed drug-naive PD patients was 5%.

According to our knowledge this is the first study evaluating the stability of the diagnosis of MCI at follow-up.

Previous studies reported older age and the higher severity of bradykinesia as clinical features associated with PD-MCI. These findings cannot be clearly discussed in relation to our results due to the small number of patients diagnosed as PD-MCI.

The evaluation of MCI in PD patients should be taken into account as a possible predictor of disease severity, has a major impact on patients' independence, patients and caregivers quality of life.

Relationship between cognitive and behavioral characteristics with demographic and motor features of patients with parkinsonian syndrome at onset

1.1 Introduction

Cognitive impairment is increasingly recognized in parkinsonian patients and especially in Parkinson disease's patients since the early stages.

Several studies evaluated the demographic and motor features of parkinsonian patients reporting advanced age, lower education, male sex, severity of motor disease, postural instability, and an akinetic-rigid syndrome as the main risk factors for cognitive impairment, expecially in PD patients [46-49].

Considering PD patients, one longitudinal study observed a 52% prevalence of dementia with over 4-years follow-up and 60% (95% confidence interval, 54–66%) prevalence of dementia with over 12-years follow up in 233 patients with PD [46] and an incremented 65% risk of dementia by age 85 years [46]. Furthermore, some studies demonstrated that cognitive disturbances in PD patients cannot be attributed to drug treatment, but are likely to be directly related to the pathology of the disease [48].

3. 6 Results

Progressive cognitively impaired patients showed higher age at onset, UPDRS at T0 and at T1, and HY score compared to not impaired patients (Table 5).

Discussion

Several studies reported an association between higher age at onset and a worst motor phenotype (higher UPDRS and HY, bradikinetic-rigid type) and cognitive impairment.

Our study confirm these data and report an even worser motor phenotype in patients with a progression to dementia.

Relationship between cognitive and behavioral characteristics of the parkinsonian syndrome with sleep and autonomic features

1.2 Introduction

Primary sleep disorders such as REM sleep behaviour and sleep breathing disorder are common non-motor symptoms in parkinsonian patients.

REM sleep behaviour disorder is a sleep parasomnia characterized by dream-enacting behaviours, often violent and injurious, occurring during REM sleep and associated with loss of the physiological REM muscle atonia [50]. According to the second edition of the ICSD, a clinical diagnosis of RBD can only be made when a patient displays violent, potentially violent or sleep-disruptive dream-enactment behaviour along with REM sleep without atonia (RWA) as determined by VPSG. This condition may be either idiopathic (iRBD) or associated with another neurologic disorder [51]. RBD affects about 33–46% of PD patients [52-53],75% of DLB patients [54], and almost 100% of MSA patients [55].The onset of RBD can precede, by years, the onset of these diseases [57-59]. For this reason several studies have tried to disclose signs predictive of the future development of a neurodegenerative disease in patients with iRBD by means of clinical, neuropsychological, electrophysiological and neuroradiological modalities. Several studies have investigated whether presence of these dysfunction in iRBD predicts the subsequent development of a neurodegenerative diseases.

Cognitive impairment has been widely evaluated in patients with iRBD patients. In general, attention, executive functions, episodic verbal memory (mainly free recall capacities), and non-verbal learning are the most affected domains in iRBD [60-65]. Additionally, some studies reported in iRBD anomalies in visuospatial/visuoperceptive abilities [60, 64-65], but this remains controversial [62-52]. However, results vary across studies depending on which cognitive domain is impaired. Population heterogeneity, small sample size, and the use of different cognitive tasks with variable sensitivity to detect deficits and variable specificity to a cognitive domain may explain these discrepancies. Infact, the presence of visuospatial (or non-verbal learning) impairment appears to be related to the extent of cognitive decline in iRBD patients [58, 65- 66], as reported in RBD-associated neurodegenerative diseases such as PD or DLB [54,63]. On the other hand, language and praxis appear to be well preserved in iRBD, although these functions have received little research attention.

Sleep-disordered breathing is characterized by snoring and sleep apnea of various severity. An abnormal breathing event is defined as snoring (clear inspiratory noise over the trachea), apnea

(defined as a stop in airflow of at least 10s, complete cessation of airflow ≥10 s), or hypopnea (reduction of 50% of the flow, with an oxygen desaturation of >4% and lasting at least 10s; ≥ 50% decrease in airflow >10 s). The snoring and apnea/hypopnea indices, i.e., average number of respective events/hour of sleep, serves to quantify sleep-disordered breathing. By convention, a snoring index ≥10 defines the presence of snoring, and an apnea/hypopnea index ≥10 defines the presence of sleep apnea. The number of apneic events is calculated as the apnea/hypopnea index (AHI),i.e., the total amount of apneas and hypopneas per hour of sleep. An AHI lower than five identifies a normal subjects, an AHI between 5 and 15 identifies mild OSA, an AHI between 15 and 30 a moderate OSA and an AHI greater than 30 a severe OSA [50].

Several studies suggest that apnea recurrence, sleep fragmentation, day- time sleepiness, and nocturnal hypoxemia may induce an impaired cognitive function in OSA patients [67-70] affecting vigilance, attention, psychomotor performance, executive function and memory [71-73]. However, the presence and the extent of the cognitive changes in OSA subjects is still a matter of debate [74-75]. Results of studies on cognitive function in OSA are heterogeneous, the controversial results may be partially explained by the severity of the disease, a minor cognitive impairment present in mild cases [76-78] and a greater deficit particularly in terms of executive function [71,79] in severe cases.

Only one study [80] evaluated the impact of sleep disorders (through VPSG) on non-motor symptoms in patients with Parkinson disease (PD) (through questionnaire and global scale) and concluded that having sleep disorders (particularly RBD and RLS but not OSA) was a predictor of overall non-motor symptoms in PD.

Considering autonomic features, orthostatic hypotension (OH) is the cardinal sign of sympathetic neurocirculatory failure. It is defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg or, in diastolic BP (DBP) of at least 10 mmHg, within three minutes of standing up or head-up tilt to at least 60° on a tilt table [81].

OH can be caused by vascular, pharmacological or neurogenic factors (nOH). nOH can be related to preganglionic neurodegenerative disease, i.e. multiple system atrophy (MSA), or to neurodegenerative postganglionic disease, i.e. Parkinson's disease (PD), pure autonomic failure (PAF), autoimmune autonomic ganglionopathy (AAG) associated with antiacetylcholine receptor antibodies (AchR) or to metabolic disease.

Considering that several disorders occur with OH, CI or both, regardless of the aetiology, many studies have been conducted in order to define the increased coexistence of the two conditions and

their causal relationship [37]. Although their identification could be relevant for diagnostic, prognostic and therapeutic outcomes, the results of these studies remain controversial [37].

2.7 Method

All patients underwent a full night VPSG including EEG (C3-A2, O2-A1, CZ-A1), right and left electro-oculogram (EOG), surface EMG of mentalis, bilateral wrist extensor and tibialis anterior muscles, EKG, microphone, oro-nasal, thoracic and abdominal respirograms, systemic arterial pressure, oxygen saturation and continuous audiovisual acquisition. A sleep laboratory technician monitored each recording. Sleep stages and tonic and phasic components of REM sleep were scored according to the American Academy of Sleep Medicine (AASM) criteria. According to ASSM and the ICSD (ICSD, 2005) criteria, we evaluated:

- arousal events: the number of arousals and the arousal index (AI) (index: number of events per hour of sleep);
- respiratory events: number of obstructive/central/mixed apnoeas/hypopnoeas and apnoea/hypopnoea index (AHI)
- movement events: PLMS, PLMS index, PLMS/arousal index; excessive fragmentary myoclonus (EFM), hypnic jerks (HJs) and RBD.

PLMS and other simple (EFM, HJs) or complex motor events during sleep (RBD) were checked against the video recording. The tonic and phasic components of REM sleep were scored separately, according to AAMS criteria. Each 30-second epoch was scored as tonic or atonic depending on whether tonic chin EMG activity was present for more or less than 50% of the epoch. In each patient, phasic EMG activity was evaluated in mini-epochs of 3 seconds in all REM sleep periods; a phasic EMG event was defined as any burst of EMG activity lasting 0.1-5.0 seconds with an amplitude exceeding at least 4 times the background EMG activity. Each VPSG was scored by a neurologist blinded to the clinical diagnosis.

All patients underwent the evaluation of autonomic control of the cardiovascular system through cardiovascular reflex tests. Orthostatic hypotension (OH) was defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg or, in diastolic BP (DBP) of at least 10 mmHg, within three minutes of head-up tilt to at least 60° on a tilt table during tilt test according to international diagnostic criteria [81].

3.7 Results

9/55 patients showed RBD. Of these 9 patients, 5 (1 PS, 1 MSA, 3 PD) were not cognitively impaired and 4 (1 PD, 3 PS) showed a progression of cognitive impairment.

5/55 patients were affected from OH. Of these 5 patients, 3 (1 PS, 1 MSA, 1 PD) were not cognitively impaired and 2 PS showed a progression of cognitive impairment.

10 patients were affected from OSA. Of these 10 patients, 5 (3 PS, 2 PD) were not cognitively impaired, of these 3 presented an improvement of OSA; and 5 (1 PSP, 1 PS, 3 PD) showed a progression of cognitive impairment, 4 presented an improvement of OSA.

Discussion

Several studies [reviewed in 37] addressed the question of the relationship between cognitive impairment and OH in the parkinsonian syndrome reporting no association between the two. Similarly our study did not disclose an association between progressive cognitive impairment and OH.

On the contrary, studies addressing the question of the relationship between cognitive impairment and RBD reported a striking specificity of idiopathic RBD in converting to parkinsonism or dementia after a range of onset from 14 to 29 years. No study discussed the relation between RBD and cognitive impairment at the onset of parkinsonian syndrome. In our sample the disease duration is 19 months and that our study assess the presence of RBD trough both VPSG and sleep questionnaire reporting a prevalence of 16% (9/55 patients), 4 of these patients presented a slightly progressive cognitive impairment.

Similarly OSA was not associated with a diagnosis of cognitive impairment.

In this study, progression of cognitive impairment is not associated to OH nor RBD or OSA.

Relationship between cognitive and behavioral characteristics of the parkinsonian syndrome with depression

1.3 Introduction

Neuropsychiatric symptoms including depression, anxiety, apathy and psychosis [36] are common in parkinsonian patients, affecting the majority of patients at some time during the course of disease. Among the most common, and most important, neuropsychiatric symptoms are depression, anxiety, apathy and psychosis [82].

In Parkinson's disease (PD), apathy has a high prevalence, ranging from 17 to 70% [83]. Although apathy and depression have been clearly dissociated as independent syndromes in PD [84], symptoms of apathy and depression may also overlap [85].

Depression is twice as common in patients with PD as in healthy controls,4 affecting 31% of patients [85] ; it may predate the onset of motor impairment [86].

Similarly, manifested neuropsychiatric symptoms are common in parkinsonian syndromes.

CBD patients are mostly depressed and the majority of them may manifest apathy, irritability and agitation at onset or during the course of the disease.

In several small studies examining the neuropsychiatric symptoms in PSP, results have mirrored those exhibited by apathetic patients with dementias of the frontal lobe [36]. For example, negative symptoms (i.e., apathy, aspontaneity, and indifference) can dominate the neuropsychiatric profile of these PSP patients, with apathy being the most common negative symptom [36] . Depression is another common symptom in PSP, although rates vary among studies [87].

Patients with CBD showed significantly more depression than both patients with PSP and controls; conversely, patients with PSP were more apathetic [87, 88] .

Less common neuropsychiatric symptoms include anxiety and irritability [87,88]

According to literature, MSA patients showed less common neuropsychiatric symptoms if compared with the other parkinsonian syndromes [89].

3.8 Results

At T0 15 patients (6 PD, 2 PSP, 2 CBS, 1 MSA, 4 PS) were depressed according to BDI. Of these patients, 8 (1 juvenile PD, 2 PSP, 3 PS, 1 MSA, 1 CBS, 2 PSP) patients remained depressed at T1.
At T0 8 (7 PD, 1PS) patients reported pathological results at STAI-1 and 7 (4 PD, 2 PS, 1 CBS) patients at STAI-2. 3 PD patients reported the same pathological results at T1.

At T1 10 patients (7 PD, 1 MSA, 2 PS) patients reported pathological results at STAI-1 and 12 (8 PD, 3 PS, 1 MSA) patients at STAI-2.

Apathy was diagnosed in 2 patients (1 PS, 1 CBS).

Discussion

Our results showed that depression was more common in patients with parkinsonian syndrome while anxiety was more common in patients with PD.

4. Conclusion

Several characteristics of parkinsonian syndrome have been evaluated in order to find a predictor of correct diagnosis early in the course of the disease. According to our finding the different feature of parkinsonian syndrome could not be useful as a predictor of a correct diagnosis but each non motor domain will help to clarify and characterize the motor syndrome. In particular, the evaluation of cognitive impairment will help to clarify the diagnosis, especially in typically clinical presentation, to define the atypical presentation in clinical heterogeneous syndrome and to stratify the prognosis according to the severity of the disease.

Furthermore, cognitive impairment has been related to different features of parkinsonian syndrome (older age at onset, worst motor phenotype, associated sleep and autonomic dysfunction, genetic background) probably related both to different pathways and to advanced stage of neurodegeneration.

In conclusion, the diagnosis of parkinsonian disorders lies in building a clinical profile in conjunction with other clinical characteristics such as mode of presentation, disease progression, response to medications, sleep and autonomic features. Taken together, these clinical features will aid the clinician in making an accurate antemortem diagnosis and hence a prediction of underlying pathology.

5. Appendix

5.1 Tables

5.2 Figures

Table 1. Diagnostic criteria of parkinsonian syndromes.

	PD	PSP	CBD	MSA	LBD
Inheritance				Sporadic	
Age at onset		40 or later		>30 y	Progressive
Onset	Progressive	Progressive	Progressive	Rapidly Progressive	
Disease duration	3 years at least	Postural instability with falls < 1 yr disease onset		Postural instability within 3 y of motor onset	
Motor signs	Clinical course of 10 ys or more	Early dysphagia & dysarthria		Dysphagia within 5 y of motor onset	
	Asymmetric onset Resting tremor	Symmetric akinesia or rigidity proximal> distal	asymmetric onset	bradykinesia with rigidity, tremor, or postural instability	parkinsonism
	Bradykinesia		akinetic rigid syndrome	gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction	bradykinesia with rigidity, tremor, or postural instability
	Rigidity			Dysphagia	
				Severe dysarthria and dysphonia	
				Pathologic laughter or crying	
		Either vertical supranuclear palsy or both slowing of vertical saccades	limb dystonia	Orofacial dystonia	
				Disproportionate antecollis	
		early dysphagia & dysarthria		Camptocormia	
				Pisa syndrome	
		abnormal neck posture retrocollis		Postural instability	
			reflex myoclonus focal myoclonus	Jerky, myoclonic postural/action tremor	
				Contractures of hands or feet	
				Babinski sign with hyperreflexia	

Table 2. Secondary causes of parkinsonism

Diagnosis	Etiology
Medication induced	*Neuroleptics*
	Lithium
	Valproic acid
	Calcium channels blockers
Structural	*Vascular (vascular parkinsonism)*
	Subdural haematoma
	Trauma (dementia pugilistica)
	Normal pressure hydrocephalus
Toxins	*Manganese*
	Carbon monoxide
	MPTP
	Carbon disulfide
	Mercury
	Cyanide
	Methanol
	Organophosphates
	Solvents
	Pesticides
(Post) infectious	*HIV*
	Measles
	Encephalitis lethargica
	Epstein–Barr virus
	Japanese encephalitis
	West Nile virus
	Coxsackie B virus
	Neurosyphilis
Metabolic	*Hypoparathyroidism*
	GM1 gangliosidosis
	Hypothyroidism
	Addison's disease
	Uraemia
	Hypoxia
	Carbon monoxide

Table 3. Description of cognitive and behavioral evaluation

Function		Test	Range	Reference
Global Cognition		MMSE	0-30; cut-off: > 22	Folstein et al, 1975
		Brief Mental Deterioration Battery		Gallassi et al., 1986, 2002, 2008
		Raven Progressive Matrices	0-38; cut- off	
Memory		Rey's 15 words: immediate recall	0–75; cut-off: >28.53	Carlesimo et al., 1996
		Rey's 15 words: delayed recall	0–15; cut-off: >4.69	Carlesimo et al., 1996
		Paired-associated word learning test	0–22.5; cut-off: >8.73	De Renzi et al., 1977
		Immediate visual memory	0–22; cut-off: >13.85	Carlesimo et al., 1996
	verbal working memory	Forward verbal span	0–9; cut-off: > 4,26	Monaco et al., 2012
		Backward verbal span	0–8; cut-off: > 2,65	Monaco et al., 2012
Attention		Barrage test	result: cut-off: <2.5	Gallassi et al., 1986, 2002
		Stroop test: time	cut-off: ≤ 27.5	Caffarra et al., 2002
		Stroop test: errors	cut-off: ≤ 7.5	Caffarra et al., 2002
		Trail Making Test A	0-infinite; cut-off: <93	Giovagnoli et al, 1996
Language	*fluency*	Verbal Fluency: phonemic	0–infinite; cut-off:>17.35	Carlesimo et al., 1996
		Verbal Fluency: semantic	0–infinite; cut-off: >25	Novelli et al., 1986
	comprehension	Token Test		
Visuo-spatial function		Rey-Osterrieth complex figure copy	0-36; cut-off:≥ 28,87	Caffarra et al., 2002
		Rey-Osterrieth complex figure recall	0-36;cut-off: ≥ 9,46	Caffarra et al., 2002
		Judgement of line orientation	0-30; cut-off <18	
	working memory	Corsi Block Test	0–9; cut-off: > 3,46	Monaco et al., 2012
Executive function		Simple Verbal Analogies Test	0–20; cut-off: >13,92	Gallassi et al., 1986; 2002; 2014
		Trail Making Test B	0-infinite; cut-off: <282	Giovagnoli et al, 1996
		Trail Making Test B-A	0-infinite; cut-off: <186	Giovagnoli et al, 1996
		Wisconsin sorting card test	0-infinite; cut-off: >0	

Table 3. Description of cognitive and behavioral evaluation

	Digit symbol test	0-infinite; cut-off<34	
Praxis	Bucco-facial and trunk praxis	0-20; cut-off:> 16	Spinnler et al., 1987
	Ideomotor praxis	0-20; cut-off: >16	Spinnler et al., 1987
	Ideative praxis	0-20; cut-off: >16	Spinnler et al., 1987
Constructional Praxis	Copy design: simple	0–12; cut-off: >7.18	Carlesimo et al., 1996
Cortical sensibilities	Digital agnosia	0-24; cut-off: > 13,75	Spinnler et al., 1987
	Neuropsychiatric Inventory		
Behavioral assessment			
	Beck Depression Inventory	0-30; cut-off: >9	
	STAI trait and state	0-infinite; cut-off :>50	
	Apathy scale	0-72; cut-off: >44	
	Evaluation of impulsive control disorder through (nMIDI)		

Table 4. Characteristics of drop-out patients.

Patient number	Sex	Age at onset (years)	Age at first evaluation (years)	Disease duration at T0 (months)	UPDRS at T0
23	2	40	42	24	8
29	1	44	45	12	17
30	1	68	69	12	24
47	1	72	74	24	30
52	1	50	48	18	10
58	1	71	73	24	28

Legend: 1 male; 2 female.

Table 5. Demographic and clinical data

Group	Sex	Education (years)	Age at onset (years)	Disease duration at T0 (months)	UPDRS T0	UPDRS T1	LED T0	LED T1
Whole Sample	35 M/20 F	10,62 ±4,46	58,56±10,50	19,03±9,8	18,48±8,67	20,74±3,21	78±167	298±169
Cognitively normal								
Whole (37)	22 M/15 F	12,20±4,14	57,37±11,20	18,32±10,32	17,41±7,88	17,54 ±9,80	44±125	269±174
PD (28)	17 M/11 F	12,65±4,14	57,57±12,08	16,17±9,79	15,51±6,96	13,84±5,15	35±107	223±114
PS (9)	5 M/4 F	13,20±4,21	56±9,31	25±10,17	23,11±8,59	29,12±12,63	72±158	373±249
Progressively cognitively impaired								
Whole (18)	13 M/5 F	8,20±4,08	61±8,2	20,5±8,48	20,61±9,78	26,61±16,45	152±225	354±149
PD (11)	8 M/3 F	10,24±4,13	61,90±7,71	17,72±9,12	16,34±8,72	18±10,87	119±205	345±154
PS (7)	5 M/2 F	7,50±2,26	59,57±9,46	24,85±5,39	27,28±7,69	40,14±14,85	215±266	370±166
PD-MCI	2 M	14±2	58±4,24	21,5±20,50	18±12,72	23,5 ± 21,92	300±424	510±127

Table 6. Neuropsychological evaluation at T0

	WHOLE SAMPLE		NOT IMPAIRED PD		PS		IMPAIRED PD		PS		MSA		CBD		PSP	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
education	10,62	4,46	12,65	4,14	13,20	4,21	10,24	4,13	7,50	2,26	5		10,5	7,78	3,50	2,12
age at T0	60,03	10,37	57,12	10,83	56,60	12,34	63,71	9,81	59,33	8,66	61		65,5	12,02	66,00	1,41
MMSE	27,17	2,05	28,06	1,27	27,56	0,90	26,73	2,07	27,79	1,35	28,27		26,305	2,84	21,65	3,18
FR BBDM	1,65	0,96	2,26	0,61	2,50	0,69	1,32	0,83	1,06	0,73	1,12		1,74	1,43	-0,43	0,08
STVM	40,36	9,38	46,58	9,22	43,15	6,93	36,41	8,30	38,27	4,41	46,4		40	7,07	25,58	11,99
LTVM	7,71	2,62	9,10	2,57	8,89	2,79	6,47	2,43	6,75	2,29	9,2		9,2	1,56	6,45	0,92
IVM	18,79	2,44	19,80	1,35	20,43	1,05	18,42	2,53	17,91	2,29	13,4		19,1	3,96	19,00	11,31
Barr T	55,35	22,24	46,18	11,34	42,80	8,20	56,24	18,99	59,83	25,10	65		122,5	45,96	70,00	4,84
Barr P	11,19	1,91	11,71	1,40	11,20	1,64	11,24	1,67	10,50	1,87	12		12,5	0,71	6,50	1,41
Barr E	0,98	2,26	0,41	0,71	0,60	1,34	0,62	1,60	3,33	5,09	4		0	0,00	3,00	0,71
Barr R	0,68	2,54	-0,38	0,75	-0,13	1,32	0,38	1,78	3,53	5,43	4,18		2,105	1,38	3,09	4,24
SCD	10,66	1,83	11,19	0,82	11,31	0,66	10,84	1,49	11,25	1,01	7,9		6,175	4,07	6,50	4,95
SVAT	15,81	2,42	16,73	1,27	17,70	1,45	14,98	3,01	14,69	1,48	15,53		18,38	0,20	12,94	4,24
WF	30,71	10,17	37,24	9,94	35,70	10,45	26,57	8,94	29,47	6,65	27,3		25,65	4,60	16,58	4,18
FS	41,09	9,16	47,06	7,45	40,40	6,58	37,10	8,96	40,33	8,07	49		43	16,97	20,00	3,57
Stroop T	23,17	14,04	17,09	5,15	15,20	7,16	25,52	13,94	27,54	10,57	36,5		35,875	30,23	37,75	2,21
Stroop E	2,49	6,62	0,15	0,49	-0,20	0,27	3,65	8,72	1,48	2,69	-1		7,29	8,90	17,00	6,61
WCST	-2,00	10,61	-5,25	16,10	-0,33	1,96	0,60	3,01	4,05				0			
RF copy	33,97	4,19	34,25	2,78	35,29	0,56	35,96	1,37	30,50	7,43			34,08			
RF recall	19,57	5,49	24,13	3,66	20,69	2,01	19,39	5,63	14,67	6,22			19,03			
FS	6,65	1,15	6,75	1,94	5,92	1,42	6,46	0,75	7,25	0,50			6,5			
BS	4,76	1,31	5,17	1,17	5,33	1,53	4,67	1,21	4,20	1,79			4			
CS	4,86	0,96	5,17	1,34	5,50	0,66	4,79	0,68	4,20	1,02			5			
TMT A	42,19	20,06	49,60	27,15	39,67	6,11	31,20	16,45	39,38	16,86			79			
TMT B	68,28	42,53	68,60	49,94	62,33	14,19	48,40	44,56	88,75	55,79			102			
TMT B-A	26,78	32,61	27,20	40,70	19,33	16,17	23,20	36,08	37,25	45,09			23			
PAW	10,36	4,88	13,24	4,73	15,46	1,74	8,14	3,51	7,05	5,36			10,55			
BL	25,45	3,41	26,40	2,30	28,00	1,73	26,50	2,07	21,40	4,16			27			
MP	29,73	3,19	31,60	1,65	31,77	1,82	28,95	4,00	27,72	3,57			28,9			
Token	32,84	2,26	32,73	3,09	31,63	4,07	33,17	2,11	32,85	1,98			33,8			
FAB	15,76	2,26	16,82	1,85	15,95	1,06	15,62	3,50	14,98	1,65			14,9			

Table 7. Neuropsychological evaluation at T1

| | NOT IMPAIRED | | | | | | IMPAIRED | | | | | | | | | |
| | WHOLE | | PD | | PS | | PD | | PS | | MSA | | CBD | | PSP | |
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
age at T1	60,87	11,87	56,09	13,77	58,20	12,40	65,19	9,65	60,17	8,30	62,00		66,50	13,44	66,50	2,12
MMSE	27,57	2,23	28,37	1,40	28,58	2,38	27,53	2,18	27,66	1,32	26,27		24,01	3,26	22,65	4,60
FR BBDM	1,70	0,97	2,25	0,73	2,22	0,46	1,38	0,84	1,36	0,90	1,21		2,39		-0,46	0,13
STVM	42,57	9,71	46,07	6,24	40,65	5,46	40,18	11,01	43,79	6,54	49,25		43,40	9,05	19,68	3,64
LTVM	8,04	2,68	8,01	2,74	8,11	2,58	8,08	2,40	8,16	2,35	10,40		10,35	1,06	5,45	0,49
IVM	19,39	2,64	20,80	1,27	20,30	1,75	18,23	2,77	20,70	3,23	16,55		18,45	1,06	13,78	0,49
Barr T	56,85	27,38	45,22	15,80	33,80	6,46	59,57	24,66	61,33	2,02	110,00		91,00	0,21	105,00	2,93
Barr P	10,43	2,21	11,17	1,77	10,40	1,34	10,38	2,06	9,17	37,85	7,00		13,00		6,50	53,74
Barr E	0,69	1,48	0,35	0,71	0,20	0,45	0,76	1,61	0,33	1,33	5,00		0,00		3,00	4,95
Barr R	0,67	2,13	-0,22	1,06	-0,68	0,73	0,78	2,16	1,09	0,52	8,05		1,14		4,56	4,24
SCD	10,65	1,85	11,26	1,09	11,56	0,65	10,65	1,59	10,37	1,62	10,00		6,10		7,13	2,11
SVAT	16,27	2,94	17,93	1,76	18,05	1,38	15,34	2,98	14,66	2,45	16,50		15,00		13,00	4,28
WF	32,64	11,97	38,09	10,68	37,59	14,62	29,79	11,63	31,72	3,00	33,60		20,30	7,07	14,58	2,12
FS	41,25	9,31	45,65	8,51	43,60	7,33	38,29	7,57	42,00	11,62	44,00		29,50	2,69	30,00	3,78
Stroop T	25,63	14,07	17,66	5,20	15,50	6,04	31,90	14,70	29,25	10,88	26,50		14,50	13,44	45,75	1,41
Stroop E	2,20	6,08	0,24	1,04	0,00	0,00	2,79	6,49	4,00	12,15	0,00		0,00		15,25	39,24
WCST	-3,20	9,06	-4,96	11,30	-0,66	2,14	-0,84	1,96	2,21	10,81						
RF copy	31,82	6,17	33,39	3,19			30,76	7,69	30,15	3,13						
RF recall	17,67	7,00	21,54	5,63			15,10	7,02	16,18	2,40						
FS	5,96	1,04	5,81	1,13			5,92	1,11	5,08	1,11						
BS	4,45	1,30	4,45	0,69	3,50	0,71	4,43	2,07	7,25	2,09						
CS	4,79	0,60	4,94	0,30			4,77	0,78	5,00	1,00						
TMT A	37,96	25,75	44,13	26,35			39,00	29,71	22,50	12,73						
TMT B	82,25	58,23	66,88	34,44			102,00	72,28	128,17	46,97						
TMT B-A	53,13	44,04	57,08	45,03	29,00	42,07	60,81	30,12	53,75	51,97						
PAW	7,36	3,37	8,93	3,08			5,57	1,62	5,50	2,01						
BL	22,45	5,37	22,75	3,95			24,00	4,86	23,50	4,32						
MP	26,54	3,83	28,54	3,13			26,20	3,61	28,60	10,21						
Token	30,10	3,35	31,25	2,19			29,33	3,95	22,00	1,12						
FAB	14,68	3,51	15,99	1,84			13,54	4,60	15,00	3,88						

Table 8. Impaired test and function of brief evaluation in the whole sample

Brief battery	Progressive patients (18 patients)				Not progressive (37 patients)			
	T0	T1	T0 %	T1 %	T0	T1	T0 %	T1 %
MMSE	3	3	9,17	9,17	0	0	0,00	0,00
FR BBDM	3	5	9,17	15,28	0	0	0,00	0,00
LTVM	1	4	3,06	12,22	2	0	2,97	0,00
IVM	1	1	3,06	3,06	2	2	2,97	2,97
CD	2	4	6,11	12,22	1	2	1,49	2,97
BARR	3	6	9,17	18,33	4	3	5,95	4,46
STVM	4	4	12,22	12,22	0	1	0,00	1,49
FS	5	5	15,28	15,28	4	0	5,95	0,00
SVAT	6	11	18,33	33,61	3	1	4,46	1,49
WF	6	6	18,33	18,33	1	0	1,49	0,00
STROOP	10	14	30,56	42,78	6	6	8,92	8,92
Global impairment	3	3	9,17	9,17	0	0	0,00	0,00
Verbal Memory	4	7	12,22	21,39	3	3	4,46	4,46
Attention	10	15	30,56	45,83	9	7	13,38	10,41
Praxis	2	4	6,11	12,22	0	1	0,00	1,49
Fluency	6	7	18,33	21,39	4	1	5,95	1,49
Executive function	7	12	21,39	36,67	4	1	5,95	1,49

Table 9. Impaired test and function of comprehensive evaluation in the whole sample

Comprehensive battery	Progressive patients (7 patients)				Not progressive (13 patients)			
	T0	T1	T0 %	T1 %	T0	T1	T0 %	T1 %
MMSE	0	0	0,00	0,00	0	0	0,00	0,00
FR BBDM	0	0	0,00	0,00	0	0	0,00	0,00
STVM	0	0	0,00	0,00	2	0	3,08	0,00
LTVM	0	0	0,00	0,00	1	2	1,54	3,08
IVM	0	1	0,00	2,86	0	0	0,00	0,00
BARR	0	0	0,00	0,00	1	0	1,54	0,00
CD	0	0	0,00	0,00	0	1	0,00	1,54
SVAT	1	1	2,86	2,86	1	1	1,54	1,54
WF	0	0	0,00	0,00	2	1	3,08	1,54
FS	0	0	0,00	0,00	0	0	0,00	0,00
STROOP	1	3	2,86	8,57	3	2	4,62	3,08
WCST	3	5	8,57	14,29	8	9	12,31	13,85
RFC	0	0	0,00	0,00	0	0	0,00	0,00
FS	0	0	0,00	0,00	1	0	1,54	0,00
BS	0	0	0,00	0,00	0	0	0,00	0,00
CS	0	0	0,00	0,00	0	0	0,00	0,00
TMT	0	0	0,00	0,00	0	0	0,00	0,00
PAW	0	2	0,00	5,71	4	0	6,15	0,00
BL	0	1	0,00	2,86	0	0	0,00	0,00
MP	0	0	0,00	0,00	0	0	0,00	0,00
Token	0	0	0,00	0,00	0	0	0,00	0,00
FAB	0	1	0,00	2,86	1	0	1,54	0,00
Praxis	0	0	0,00	0,00	0	0	0,00	0,00
Cortical sensibilities	0	0	0,00	0,00	1	1	1,54	1,54
Global impairment	0	0	0,00	0,00	0	0	0,00	0,00
Verbal Memory	0	2	0,00	5,71	4	2	6,15	3,08
Attention	1	3	2,86	8,57	4	2	6,15	3,08
Praxis	0	0	0,00	0,00	0	1	0,00	1,54
Fluency	0	0	0,00	0,00	2	1	3,08	1,54
Comprehension	0	0	0,00	0,00	0	0	0,00	0,00
Executive function	3	6	8,57	17,14	9	10	13,85	15,38
Visuo spatial memory	0	1	0,00	2,86	0	0	0,00	0,00
Working memory	0	0	0,00	0,00	0	0	0,00	0,00
Praxis	0	0	0,00	0,00	0	0	0,00	0,00
Cortical sensibilities	0	0	0,00	0,00	1	1	1,54	1,54

Table 10. Characteristics of patients with RBD.

Diagnosis	CI (Y/N)	(MMSE)	Sex	Age at onset (years)	Disease duration at T0 (months)	Age at RBD onset	UPDRS at T0	UPDRS at T1
8 PS	N	27,9	1	63	55	61	22	26
12 MSA	N	26,27	2	58	52	20	31	40
21 PD	N	26,7	2	76	28	-	7	8
35 PD	N	25,7	1	68	34	69	14	15
38 PD	N	28,27	1	62	26	30	14	15
10 PD	Y	20,97	1	55	52	55	27	39
51 PS	Y	25,33	1	59	40	58	22	29
57 PS	Y	27	1	64	34	65	22	33
60 PS	Y	28,46	1	43	40	39	21	47

Legend: CI: cognitive impairment, Y: yes, N: no; MMSE: Mini Mental State Evaluation 1 male; 2 female.

Table 11. Diagnostic criteria for Parkinson Disease –Mild Cognitive Impairment (PD-MCI).

Criteria for the Diagnosis of PD-MCI	
comprehensive assessment (Neuropsychological testing that includes two tests within each of the five cognitive domains - attention and working memory, executive, language, memory, and visuospatial)	Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains Impairment on neuropsychological tests may be demonstrated by: -Performance approximately 1 to 2 SDs below appropriate norms or significant decline demonstrated on serial cognitive testing or significant decline from estimated premorbid levels
Subtype classification for PD-MCI	PD-MCI single-domain —abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired PD-MCI multiple-domain —abnormalities on at least one test in two or more cognitive domains (specify the domains)

Table 12. Comparison of cognitive deficit in parkinsonian syndromes (modified from 36, 39, 40).

Function	PD	PDD	PSP	DCB	MSA
Memory	Mild,inconstant recall deficit,	Mild-moderate information storage impairment	Impaired recall and access to stored information	Mild, inconstant episodic memory impairment	Inconsistent results
Learning	Categorization deficit, long span, implicit learning	Categorization deficit, more implicit than explicit learning deficit	Implicit procedural deficit, explicit learning deficits compensated by semantic cues	Explicit learning deficits compensated by using semantic cues	Inconsistent results
Executive functions	Mild planning; Problem solving; concept-formation; abstract reasoning	Moderate planning; problem-solving; concept-formation; abstract reasoning	Severe and early planning; problem-solving; concept-formation; abstract reasoning	Mild to moderate planning; problem solving; concept- formation; abstract reasoning	Mild planning; Problem solving; concept-formation; abstract reasoning
Language	Decreased fluency	Decreased fluency	Decreased letter fluency; transcortical motor or dynamic aphasia	Decreased semantic fluency, yes/no reversal; transcortical motor/ Broca/anomic aphasia, PPA	Decreased fluency
Praxis	No ideomotor apraxia, constructional apraxia may be present	Ideomotor apraxia may be present, but no asymmetric apraxia. Constructional apraxia	Mild ideomotor apraxia, no ideatory apraxia	Ideomotor > ideatory Apraxia, constructional apraxia	Inconsistent results
Visuo-spatial functions	Horizontal plane attention, spatial perception, visuomotor coordination spatial imagery	Mild or absent	Visual grasping; vertical plane inattention; spatial perception	Horizontal neglect; Balint-Holmes syndrome	Inconsistent results

**Table 13.** Cognitive testing in the diagnosis of parkinsonian disorders (modified from 39, 40)

	PSP	DCB	MSA
PD	Phonemic fluency	Orofacial apraxia	TMT –B E
	Semantic fluency		STROOP E
	WCST		
	TMT A time and errors		
	FAB *		
PSP		Orofacial apraxia	
MSA	Phonemic fluency	Orofacial apraxia	
	Semantic fluency		
	WCST		

Table 14. Behavioural characteristics of parkinsonian syndromes (modified from 39).

Function	PD	PDD	PSP	DCB	MSA
Apathy	+	+	+++	-	+
Depression	++	++	+	++	+
Hallucination; delusions; delusional misidentification;fluctuation	++	+++	-	-	-
Irritability	+	+	+	-	+
Dishinibition	++	++	++	-	-
Anxiety-agitation	++	++	-	-	+
Utilization, imitation, prehension behaviors	++	++	+++	-	+

Legend: -:absent; +: rare; ++:present +++:usually early and severe symptom.

Figure 1. Progression of cognitive impairment
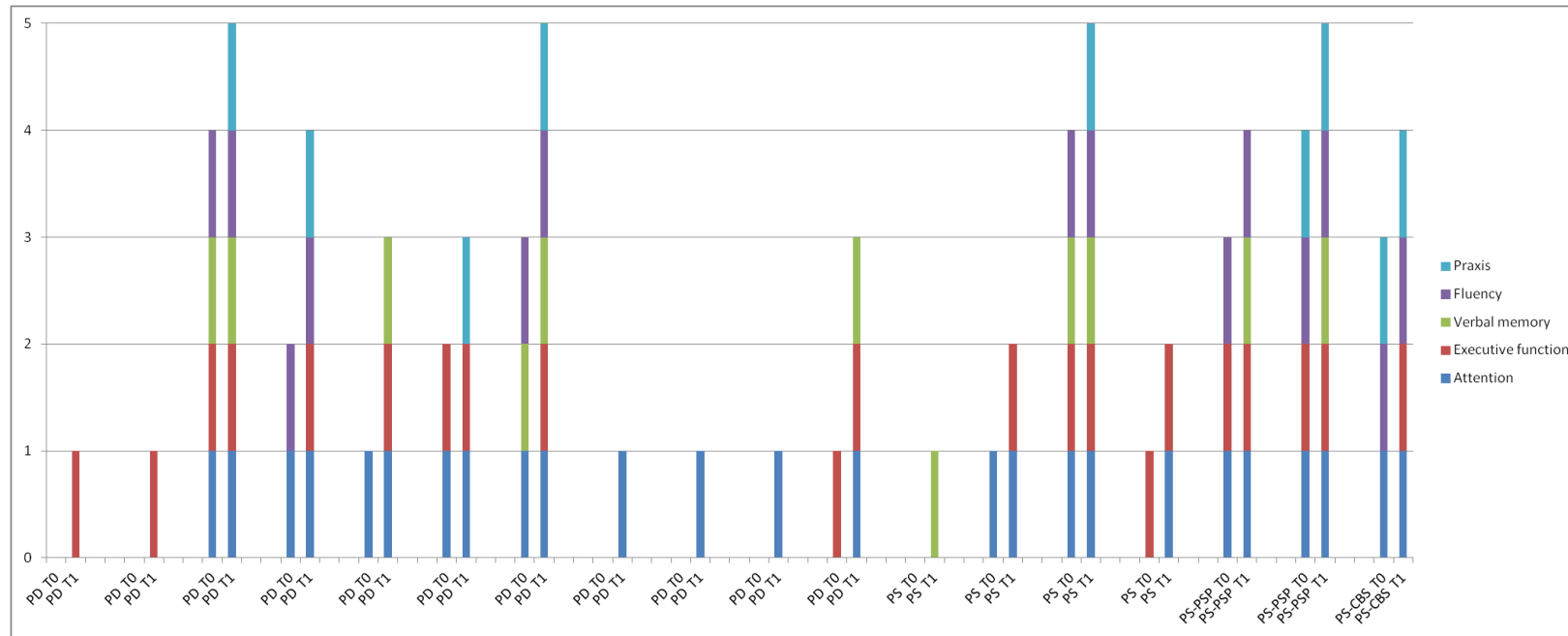
Figure 2. Percentage of patients failing each neuropsychological test in progressive (a) and not progressive (b) patients.
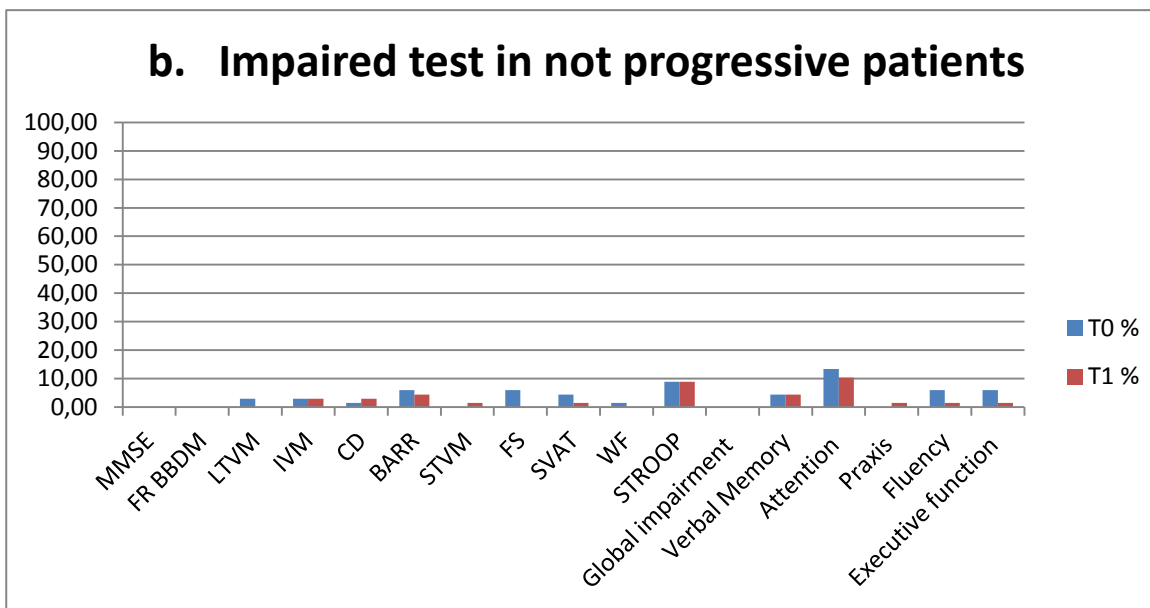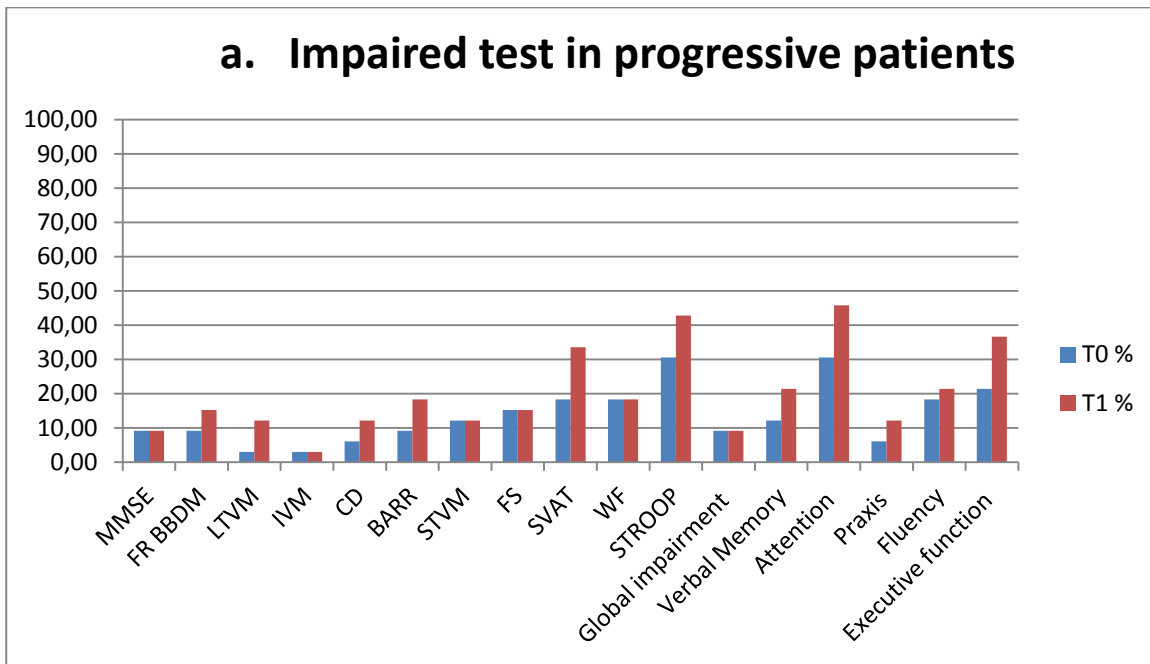
a. Impaired test in progressive patients

b. Impaired test in not progressive patients

Evolution of cognitive impairment
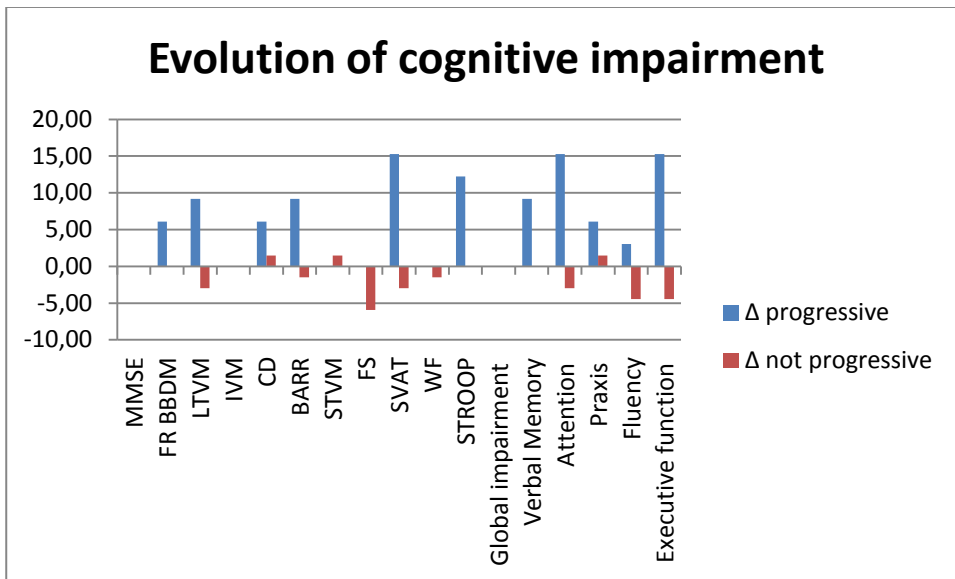
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