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TESI DI DOTTORATO IN:

Cognitive and behavioral features in atypical parkinsonian syndromes

RELATORE
Chiar.ma Prof.
Maria Teresa Pellecchia

CANDIDATA
Dott.ssa Sofia Cuoco
Matricola: 8800900015

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Abstract

Introduction

Progressive supranuclear palsy (PSP), Multiple system atrophy (MSA), corticobasal degeneration (CBD) and dementia with Lewy Bodies (DLB) are included in atypical parkinsonisms (AP) and they typically involve multisystem degeneration. Defining the neuropsychological profiles is important for a detailed intra-AP framework to identify phenotypes and for characterization of patients, but there are few studies which specifically analyz the neuropsychological and behavioral profiles of AP.

Objectives

From November 2016 to September 2019, at the University Hospital of Salerno and in collaboration, where necessary, with other Italian centers, data collection and processing work was carried out on a sample of healthy subjects (HC) and patients with movement disorders, divided into patients with Parkinson's disease (PD), Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP) and CorticoBasal Syndrome (CBS).

Specific work objectives were:

1) investigation of the neuropsychological and behavioral profile of patients with atypical parkinsonism, divided according to their respective clinical phenotypes;

2) investigation of the evolution over time of the neuropsychological and behavioral profile of patients with atypical parkinsonism;

3) identification and characterization of the alteration of global cognitive state, of mild cognitive impairment- single domain (MCI-sd), of mild cognitive impairment - multiple domain (MCI-md) and of normal cognition (NC) of patients with atypical parkinsonism;

4) comparison of neuropsychological and behavioral aspects in healthy subjects and patients with Parkinson's disease; intra-group comparison of the neuropsychological profile between PSP-Cortico Basal Syndrome phenotype and CBS and MSA-Parkinsonian and cerebellar phenotypes;

5) validation of a new language screening battery for neurodegenerative diseases;

6) investigation of language domain in the sample of patients with PSP and MSA by clinical use of the new battery for neurodegenerative diseases;

7) investigation and validation of questionnaires for assessing the quality of life in patients with PSP and their respective caregivers;
8) investigation of gender differences in MSA patients.

Sample

The sample was divided into two macro groups, such as patients and healthy subjects recruited at the University Hospital of Salerno and patients and subjects recruited for multicentric studies. In particular, at the University Hospital of Salerno we recruited 55 patients with MSA, 59 with PSP, 50 HC, 55 with PD and 5 with CBS. In multicenter studies, 162 caregivers (29 belonging to University Hospital of Salerno), 190 PSP-patients (62 belonging to University Hospital of Salerno) and 134 HC (35 belonging to University Hospital of Salerno) were recruited.

Instruments and procedure

Patients underwent a comprehensive neuropsychological and neuropsychiatric battery at baseline (T0) and 6 or 12 months follow-up (T1) evaluation, where possible. We compared patients with atypical parkinsonism with HC and patients with PD and different intra-group phenotypes.
The severity of the diseases was evaluated with the PSP rating scale (PSP-rs), the Natural History and Neuroprotection in Parkinson Plus Syndrome (NNIPPS) scale, the Unified Multiple System Atrophy Rating Scale (UMSARS) and Unified Parkinson's Disease Rating Scale part III (UPDRS-III). Cognitive and behavioral profile were evaluated with a comprehensive neuropsychological battery, following Litvan's criteria for dementia and mild cognitive impairment (MCI) in PD proposed in 2012. Using the z scores of the individual tests and a control group enrolled subjects were classified as having normal cognition (NC), MCI- single domain (MCIsd), MCI- multiple domain (MCImd) and dementia (D). Furthermore, for language domain we developed and used a Screening for Aphasia in NeuroDegeneration (SAND).
For quality of life, we translated in Italian and validated the Italian version of the PQoLCarer and PSP-QoL patients scales and we directed and analyzed the multi-center data.

Results

First of all, in order to widen the tools for the analysis of language in neurodegenerative diseases and to be able to use a more complete instrument, we implemented a screening battery, composed

of nine tests (picture naming, word and sentence comprehension, word and sentence repetition, reading, semantic association, writing and picture description).

Subsequently, comparing the neuropsychological and behavioral profile of MSA, PSP and PD patients, we found pervasive cognitive deficits, apathy and depressive symptoms in PSP, whereas little cognitive difference was found between PD and MSA. The findings indirectly supported a dysfunction of prefronto- subcortical circuitries (i.e., dorsolateral prefrontal and limbic circuits) in PSP and PD. Cognitive similarities between MSA and PD reinforced the pivotal role of altered basal ganglia and subsequent frontal deafferentation in the occurrence of the cognitive deficits.

Analyzing the PSP sample, we found that half of the cohort presented Richardson's syndrome, followed by PSP with parkinsonism and corticobasal syndrome and that the only cognitive tests differentiating the phenotypes PSP-RS and PSP-CBS were semantic fluency and ideomotor apraxia. The majority of our cohort was either affected by dementia or presented normal cognition. Richardson's syndrome presented the highest rate of dementia. The only marker of PSP non-Richardson's syndrome phenotype was a better performance in visuo-spatial testing. In PSP, mild cognitive impairment likely represents an intermediate step from normal cognition to dementia. We analyzed the language profile of several phenotypes of PSP with SAND battery and showed that the PSP-tailored SAND Global Score is an acceptable, consistent and reliable tool to screen language disturbances in PSP. We showed that language disturbances feature PSP patients irrespective of disease phenotype, but parallels the deterioration of the global cognitive function.

We applied CBS and PSP clinical diagnostic criteria to patients presenting with corticobasal syndrome and we found that PSP-CBS showed more severe clinical features compared to CBS according to the total PSP rating scale and subscores. We showed that both PSP and CBS criteria can be applied to such patients and that PSP-CBS showing a more severe form of disease in term of motor and cognitive impairment than CBS.

We worked on the translation, analysis of the psychometric properties and use of Parkinsonism Carers QoL (PQoLCarer) and PSP- QoL. We found that the scales are valid for the PSP sample and gender and geographic location presented a significant impact on the PSP-QoL in our sample with women and patients from the South of Italy scoring higher than their counterparts.

Analyzing the MSA sample data we found that at baseline assessment no patient with MSA was affected by dementia, whereas 66% of the whole MSA sample had a diagnosis of MCI. Specifically, MCI occurred in 61.9% of patients belonging to MSA-C group and in 68.9% of patients belonging to MSA-P but the comparison between MSA-P and MSA-C revealed no significant difference on any cognitive tests and apathy scale; instead, patients with MSA-P group had more reduced functional autonomy and more severe depression than patients with MSA-C. At follow-up

evaluation, we found a significant worsening in cognitive tests assessing spatial planning and psychomotor speed in MSA-C group and a significant worsening in prose memory, spatial planning, repetition abilities and functional autonomy in MSA-P group.

Comparing MSA patients by gender we found that *c*ognitive and behavioral differences in MSA involve global cognition, planning, attention, visual-perceptive skills and depression, with female patients more compromised than males. Female patients deteriorated more than men over time as for motor functions and attention.

Finally, by analyzing the language profile in MSA patients we found that the MSA tailored SAND Global Score better represents language abilities in MSA and that language disturbances feature MSA patients irrespective of disease phenotype, but parallels the deterioration of the global cognitive function. We partially contributed to a better understanding of the role of the basal ganglia in language, thanks to our preliminary and exploratory findings.