Cognitive onset Parkinson's disease or Prodromal DLB?

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Introduction

Non-motor symptoms in Parkinson's disease (PD) are widely described and variable, and often precede motor impairment by years. Among them cognitive deficit, usually considered as a late complication of disease, is described in 24-36% of patients at time of diagnosis, as defined on the basis of detailed neuropsychological test battery.
In any case it has been considered only inside an established PD.

Though, it may be the case an occasional patient asks for neurological consultation because of cognitive complaints, before any motor symptom of PD is evident. This has not been described yet.

Moreover, according to literature, such patient is more likely classified as affected by Dementia with Lewy Body (DLB), or its prodromal subtype, rather than PD in which motor features are thought to be present when cognitive complaints onset.

Methods

We present a case-series of 13 patients asking for neurological consultation because of cognitive complaints, firstly labeled as MCI and who fit the criteria for PD only years later (2.88 ± 1.82; range 0.52 – 5.78), confirmed by means of DAT SPECT.

We describe and characterize clinical, neuropsychological and functional neuroimaging (^{18}F-FDG-PET, DAT SPECT) features of these 13 patients (PD-COG), compared to a control group of 11 *de novo* PD patients (PD-MOT) without cognitive impairment (MMSE score > 27, maximum one neuropsychological test impaired) and to 18 healthy controls (HC), matched accordingly to sex, age, education and UPDRS-III score (PD-MOT only).

Results

Compared to normative data, at baseline evaluation PD-COG patients showed a multiple domain cognitive impairment, especially in episodic memory, executive functions and visual-spatial skills, which worsened when PD was diagnosed, even if MMSE remained stable (Table 1).
In comparison to PD-MOT, PD-COG performed globally worse in cognitive tasks, especially in memory recall, executive functions, attention and visuo-spatial domain (Table 2).
Since baseline PD-COG patients have been followed up for of 5.80 ± 2.93 years (range 2.12 – 12.38 y) and dementia developed in only one of them. None experienced hallucinations or cognitive fluctuations.

No significant differences were found in the direct comparison between the two PD groups on both DAT SPECT and ^{18}F-FDG-PET.

Compared to healthy controls PD-COG showed significant hypometabolism in bilateral middle temporal gyrus (BA39), supramarginal gyrus and inferior parietal lobule (BA40) in the right hemisphere, superior and middle occipital gyrus (BA19) and precuneus (BA7) in the left one (Figure 1).
Compared to healthy control group no significant clusters of brain hypometabolism were found in PD-MOT group.

TABLE 1 - PD COG vs Normative data

	BASELINE (mean ± SD)	DIAGNOSIS (mean ± SD)	p value
MMSE	27.1 ± 2.5	26.9 ± 2.3	**0.14**
Corsi Span	4 ± 0.6	3.1 ± 1.4	**0.02**
Digit Span	5.4 ± 0.8	4.6 ± 1.1	**0.07**
Babcock Story Recall Test	8.4 ± 3.6	8.2 ± 5.3	0.13
RAVLT Immediate	24.8 ± 9.3	20.5 ± 11.8	**0.04**
RAVLT Delayed	4 ± 2.7	2.4 ± 3.2	0.09
Trail Making Test A	89.7 ± 38.3	120.1± 61.2	**0.03**
Trail Making Test B-A	363.1 ± 235.3	346.2 ± 177.6	0.34
Digit Symbol	18.2± 8.2	14.7 ± 7.8	**0.05**
Stroop Color	29.7 ± 5.7	25.8 ± 9.6	**0.04**
Stroop Color Word	8 ± 3.3	7.2 ± 5.8	0.33
Clock Drawing Test	4.4 ± 4.1	5.7 ± 4.8	0.28
Simple Copy Task	8.1 ± 1.7	7.1 ± 2.3	**0.04**
Programmed Copy Task	64 ± 4.7	63 ± 5.9	0.47
Semantic Fluency	25.2 ± 7	21.8 ± 7.6	0.23
Phonological Verbal Fluency	24± 12.9	19.8 ± 7.7	0.40

TAB.1 - Comparisons in neuropsychological performance in PD-COG at baseline versus PD diagnosis time

TABLE 2

	BASELINE			DIAGNOSIS		
	PD COG (mean ± SD)	PD MOT (mean ± SD)	p value	PD COG (mean ± SD)	PD MOT (mean ± SD)	p value
MMSE	27.1 ± 2.5	28.8 ± 1.2	**0.02**	26.9 ± 2.3	28.8 ± 1.2	**0.01**
Corsi Span	4 ± 0.6	4.5 ± 0.5	**0.02**	3.1 ± 1.4	4.5 ± 0.5	**0.002**
Digit Span	5.4 ± 0.8	5.4 ± 0.8	0.5	4.6 ± 1.1	5.4 ± 0.8	**0.04**
Babcock Story Recall Test	8.4 ± 3.6	12.1 ± 3.6	**0.01**	8.2 ± 5.3	12.1 ± 3.6	**0.03**
RAVLT Immediate	25.4 ± 9.1	34.2 ± 6.7	**0.01**	20.5 ± 11.8	34.2 ± 6.8	**0.003**
RAVLT Delayed	4.1 ± 2.6	6.1 ± 1.7	**0.02**	2.4 ± 3.2	6.1 ± 1.7	**0.003**
Trail Making Test A	89.7 ± 38.3	55.7 ± 15.3	**0.01**	120.1 ± 61.2	55.7 ± 15.3	**0.002**
Trail Making Test B-A	361.4 ± 246.7	77.4 ± 57	**0.0004**	346.2 ± 177.6	77.4 ± 57	**0.0001**
Digit Symbol	18.4 ± 8.6	30 ± 9	**0.002**	14.7 ± 7.8	30 ± 9	**0.001**
Stroop Color	30.1 ± 5.8	37.3 ± 5.4	**0.003**	25.8 ± 9.6	37.3 ± 5.4	**0.002**
Stroop Color Word	8 ± 3.3	15.2 ± 4.6	**0.0002**	7.2 ± 5.8	15.2 ± 4.6	**0.002**
Clock Drawing Test	4.4 ± 4.1	5.9 ± 6.7	0.25	5.7 ± 4.8	5.9 ± 6.7	0.47
Simple Copy Task	8.1 ± 1.7	9.7 ± 1	**0.01**	7.1 ± 2.3	9.7 ± 1	**0.002**
Programmed Copy Task	64 ± 4.7	66.9 ± 3.1	**0.05**	63 ± 5.9	66.9 ± 3.1	**0.04**
Semantic Fluency	25.2 ± 7	33.6 ± 13.8	**0.03**	21.8 ± 7.6	33.6 ± 13.8	**0.01**
Phonological Verbal Fluency	24 ± 12.9	29.1 ± 8.9	0.14	19.8 ± 7.7	29.1 ± 8.9	**0.01**

TAB.2 - Comparisons in neuropsychological performance in PD-COG versus PD-MOT at baseline and PD diagnosis time

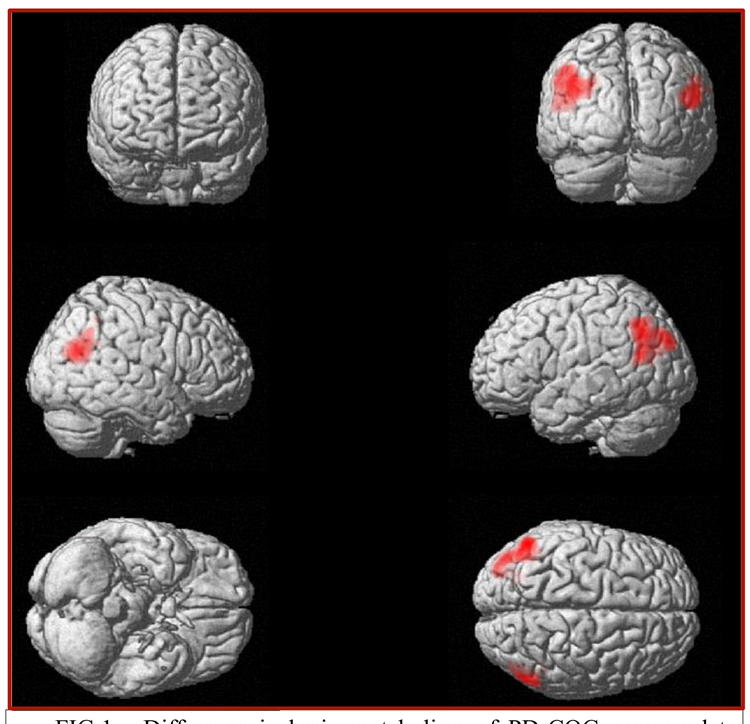

FIG.1 - Difference in brain metabolism of PD-COG compared to HC. Relative cortical hypo-metabolic areas are shown in red

Discussion

For a long time Parkinson's disease has been considered an exclusively movement disorder, associated to cognitive decline only in later stages. Nowadays, evidence shows cognitive impairment already in the earliest phase of disease. We describe a group of patients with multi-domain cognitive deficit preceding motor symptoms. In such situation, the question is open on whether these patients are affected by DLB in its prodromal stage or they are affected by PD with cognitive symptoms preceding motor ones. Indeed, present criteria do not allow the diagnosis of PD in absence of motor impairment. The answer is uncertain at the moment, although it might only be matter of semantics and these patients would be more meaningful labeled as affected by 'prodromal Lewy-body disease'.
The poor tendency toward dementia, the absence of hallucinations and fluctuations during the follow-up years favours the latter hypothesis - i.e. cognitive onset PD. This seems also supported by the absence of occipital hypometabolism which would have standed for a DLB diagnosis. Absence of metabolic changes in PD-MOT highlights that ^{18}F-FDG-PET findings strictly parallel cognitive impairment in PD. We suggest this PD-COG variant is included in Parkinson's disease spectrum, inside the umbrella of 'Lewy body diseases', agreeing that distinction between PD-MCI, PD-COG and DLB is likely arbitrary given their similarities. Obviously, this has to be confirmed in larger series in other centers.

Conclusions

Isolated mild cognitive impairment, either amnesic or non-amnesic, is a possible presentation of Parkinson's disease, just like other prodromal non motor symptoms. The general effort to intercept PD since earliest stages has the strategic role to widen therapeutical window and efficacy when specific or preventive therapies will be available.

References

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