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Clinical impact of dual-tracer FDOPA and FDG PET/CT for the evaluation of patients with parkinsonian syndromes

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Abstract

Parkinsonian syndromes include typical cases of idiopathic Parkinson's disease (PD) and atypical parkinsonian syndromes (APS) associated with cognitive and vegetative disorders, which are more challenging to diagnose. The aim of this study was to assess -the value of dual-tracer imaging 6-fluoro-(18F)-L-DOPA (FDOPA) and fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), performed in routine patients demonstrating extrapyramidal signs and cognitive complains, for the diagnosis and management of parkinsonian syndromes.

We retrospectively included 143 consecutive patients who underwent both FDOPA PET/CT (for the evaluation of parkinsonism) and FDG PET/CT (for the evaluation of cognitive complaints) in the same institution. The suspected clinical diagnosis before imaging and the final post-imaging diagnosis were collected by a dedicated questionnaire.

FDOPA was pathological in 90.2% of cases, including 74.1% of PD, 3.5% of parkinsonian dementia and 7% of APS. FDG was normal or near normal in 58.7% of patients. A pattern of diffuse cortical hypometabolism was observed in the remaining patients, more frequently in APS than in PD patients ($P = .001$). Importantly, in 7.7% of cases dual-tracer PET/CT allowed to decide between several diagnostic hypotheses and led to a new diagnosis in 14.0%. Therefore, the management of these patients was modified, with clinical re-evaluation in a specialized unit and a control of neuropsychological tests and imaging.

Dual-tracer PET/CT imaging may be a precious help in the diagnosis and management of parkinsonian syndromes.

Abbreviations: AD = Alzheimer's disease, APS = atypical parkinsonian syndrome, CBD = cortico-basal degeneration, CT = computed tomography, DLB = dementia with Lewy bodies, FDG = fluorodeoxyglucose, FDOPA = 6-fluoro-(18F)-L-DOPA, FTD = frontotemporal dementia, H&Y = Hoehn and Yahr, MSA = multiple system atrophy, PD = Parkinson's disease, PET = positron emission tomography, PSP = progressive supranuclear palsy, REM = rapid eye movement, ROI = regions-of-interest, SPM = statistical parametric mapping, UPDRS = Unified Parkinson's Disease Rating Scale.

Keywords: fluorodeoxyglucose, 6-fluoro-(18F)-L-DOPA, positron emission tomography/computed tomography, parkinsonian syndromes, diagnostic orientation

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD).[1] The typical symptomatology of parkinsonian syndrome includes akinesia associated with rigidity, resting tremor, and postural instability, secondary to bilateral chronic degeneration of the nigrostriatal pathway. In some cases, parkinsonian syndromes are so-called "atypical" (atypical parkinsonian syndrome, APS) because, in addition to motor symptoms, patients also present signs of cortical involvement (cognitive disorders, aphasia, apraxia, sensory deficit), pseudo-bulbar signs (dysarthria, dysphagia, sphincter disorders), pyramidal syndrome, cerebellar syndrome, or oculomotor disorders. The etiological diagnosis is essential to adapt the therapeutic management, but this is often difficult in early stages of the disease.

In complex or doubtful situations, it may be required to complete the clinical assessment with additional tests. In nuclear medicine, 6-fluoro-(^{18}F)-L-DOPA (FDOPA) positron emission tomography/computed tomography (PET/CT) is used to study the pre-synaptic dopaminergic pathway. FDOPA uptake reflects the integrity of dopaminergic pathway, the activity of the L-Dopa-decarboxylase enzyme and the storage capacity of dopamine.[2] Since the 1990s, several studies have shown

Editor: Barbara Palumbo.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Emsen B, Villafane G, David JP, Evangelista E, Chalaye J, Lerman L, Authier FJ, Gracies JM, Itti E. Clinical impact of dual-tracer FDOPA and FDG PET/CT for the evaluation of patients with parkinsonian syndromes. Medicine 2020;99:45(e23060).

Received: 24 May 2020 / Received in final form: 18 September 2020 / Accepted: 5 October 2020

http://dx.doi.org/10.1097/MD.0000000000023060

decreased FDOPA uptake in the striata of PD patients compared with controls.[3] A correlation between striatal FDOPA uptake and loss of dopaminergic neurons in the pars compacta of the substantia nigra has been demonstrated in animal models of PD.[4] Fluorodeoxyglucose (FDG) PET/CT has been widely applied in neurodegenerative diseases to highlight areas of reduced glucose metabolism, as a consequence of neuronal destruction or resting,[5] which usually precede morphological atrophy. The topography of these areas of hypometabolism makes it possible to orient towards different APS, such as cortico-basal degeneration (CBD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP) or multiple system atrophy (MSA).[6,7]

Aim of our work was to study the value of dual-tracer imaging FDOPA and FDG PET/CT, performed in routine patients demonstrating extrapyramidal signs and cognitive complains, for the diagnosis and management of parkinsonian syndromes.

2. Patients and methods

Between October 2013 and March 2017, we included all consecutive patients referred by neurologists or gerontologists, who underwent both FDOPA PET/CT (for the evaluation of extrapyramidal signs) and FDG PET/CT (for the evaluation of cognitive complains) in the same institution, and within 6 months from each other. Patients who did not undergo both PET/CT within 6 months or in whom image quality was insufficient for review were excluded. In total, 286 PET/CT acquisitions were available in 143 patients. Access to clinical information and retrospective analysis of imaging data acquired in routine clinical care in patients with parkinsonian syndrome was approved in April 2019 by the Institutional Review Board of Henri Mondor University Hospitals (#00011558).

2.1. Collection of clinical data

Socio-demographic data such as sex and age at imaging were retrospectively collected for each patient. The presence of a typical akineto-rigid parkinsonian syndrome or tremor, cognitive disorders, executive disorders, hallucinations, Unified Parkinson's Disease Rating Scale (UPDRS), Obeso and Hoehn and Yahr (H&Y) scores were also collected, when available. For each patient, qualitative results of neuropsychological tests were also recorded. The suspected clinical diagnosis before imaging and the final post-imaging diagnosis retained by the clinician were collected by a dedicated questionnaire.

2.2. Imaging protocols

For FDOPA PET/CT, fasting patients were asked to interrupt dopaminergic treatments (12 hours) whenever possible and 100 mg of Carbidopa were administered. They were injected with 2.5 MBq/kg (0.07 mCi/kg) FDOPA and image acquisition started 90 min later. For FDG PET/CT, fasting patients were put in neurosensory resting for 10-15 min and were injected with 2.5 MBq/kg (0.07 mCi/kg) FDG; image acquisition started 30 minutes later.

All 286 PET/CT exams were performed on a Gemini GXL16 camera (Philips, Da Best, The Netherlands) at Henri Mondor University Hospitals. A brain CT (100 kV, 220 mAs) without iodinated contrast agent was performed for attenuation correction and anatomical localization, followed by a PET emission step of 15 minutes in 3D mode. PET images were reconstructed, with and without attenuation correction using an iterative algorithm.

2.3. Image analysis

Each exam was read by consensus of 2 nuclear physicians after proper reorientation in the anterior commissure-posterior commissure plane and normalization of color scale on the basal ganglia. For FDOPA PET/CT, visual interpretation was performed according to Benamer et al.[8] (Fig. 1). Briefly, a postero-to-anterior decrease of uptake, symmetrical or asymmetrical, bilateral or unilateral, was considered pathological. Semi-quantitative analysis was then performed to measure the specific-to-nonspecific FDOPA uptake ratios. Briefly, after staggered summation of 10 axial slices covering the striata, three 18-mm-diameter circular regions-of-interest (ROIs) were placed on each striatum, over the caudate nucleus, the anterior and the posterior putamen, on the right and the left sides (total: 6 ROIs) and a large occipital ROI for the reference background.[8] Specific-to-nonspecific ratios and asymmetry index were calculated as previously described.[9] For FDG PET/CT, cortical and

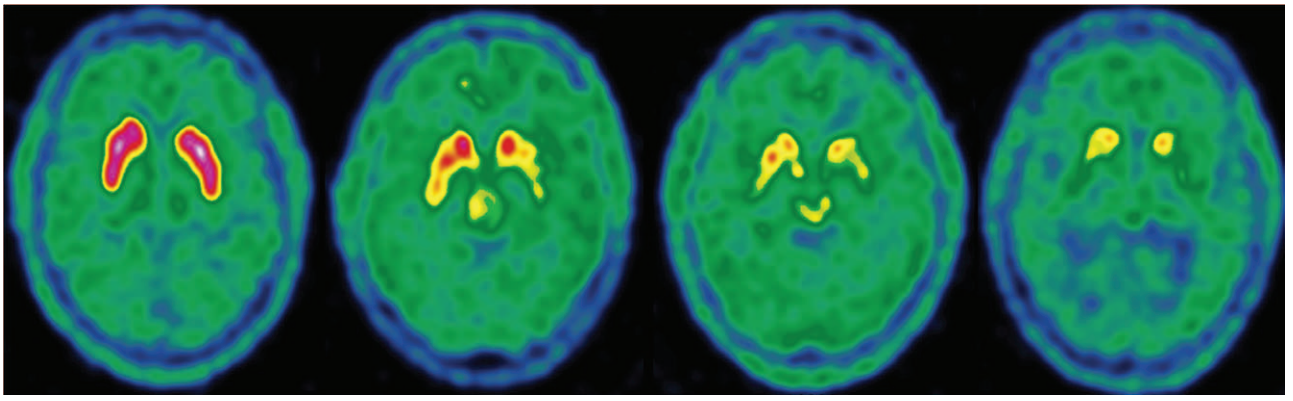

Figure 1. Representative example of Benamer grades, adapted to FDOPA uptake.[8] FDOPA = 6-fluoro-(18F)-L-DOPA.

Table 1

Classification into 4 categories of uptake pattern observed in FDG PET/CT.

0	Normal
1	Anomaly of the amygdalo-hippocampal complexes (in some cases, a small isolated cortical anomaly was associated, interesting the superior parietal territory or the precuneus)
2	Diffuse cortical involvement (occipital junction territory included) without abnormality of the posterior cingulate gyrus (PCG, region affected in priority in the AD)
3	Diffuse cortical involvement (occipital junction territory included) with PCG anomaly
4	Diffuse cortical involvement including occipital cortex (primary visual area) +/− PCG involvement

AD = Alzheimer's disease, PCG = posterior cingulate gyrus.

subcortical uptake was evaluated visually and patients were classified into 5 categories according to the pattern of hypometabolism (Table 1).

2.4. Statistical analysis

Analyzes were performed with MedCalc software version 12.2.1 (Stata Inc., College Station, TX). Non-normal distribution of variables was checked by Kolmogorov-Smirnov test. Categorical variables were compared using the Fisher's exact test. Quantitative variables were compared using the Mann-Whitney or Wilcoxon tests (for unpaired and paired data, respectively). APS group included patients with DLB, MSA, CBD, or PSP, and excluded patients for whom a diagnostic doubt persisted between a DLB and parkinsonian dementia, after the two PET/CT examinations. PD group excluded patients with Parkinson dementia. A bilateral $P < .05$ was considered significant.

3. Results

3.1. Population characteristics

Clinical characteristics are described in Table 2. The study included a majority of men (61.5%) and ages ranged 41-97 years. The mean duration between first clinical appointment and first imaging (FDOPA or FDG) was 27.2 ± 18.0 months. Among the 96 patients in whom an H&Y score was available, 74% had a score ≤ 2, only 1 had a score of 4, and none had a score of 5. Most patients had a predominantly akineto-rigid parkinsonian syndrome compared to a pure tremor form (82.5% vs 25.2%, respectively). Despite all patients had cognitive complains, only 23.8% of them had cognitive impairment on neuropsychological tests and 4.2% of them had visual hallucinations.

Table 2

Characteristic of the studied population.

Characteristic of the population	Number (n)	Percentage (%)
Total	143	100
Woman	55	38.5
Man	88	61.5
Mean age	66	
Standard deviation (SD)	9,6	
Hoehn and Yahr in OFF (n = 96)		
H&Y = 0	13	13.5
H&Y = 1	15	15.6
H&Y = 2	43	44.8
H&Y = 3	24	25
H&Y = 4	1	1
H&Y = 5	0	0
Akineto-rigid syndrom	118	82.5
Tremor	36	25.2
Both of them	21	14.7
Cognitives disorders	34	23.8
Visual hallucinations	6	4.2

H&Y = Hoehn and Yahr, SD = standard deviation.

3.2. FDOPA PET/CT

Among the 143 patients included, 90.2% demonstrated pathologic FDOPA uptake (Table 3). A final diagnosis of PD was given in 74.1%, an APS in 7.0%, a parkinsonian dementia in 3.5%, an inconclusive diagnosis (doubt between parkinsonian dementia or DLB) in 3.5%, an akinetic-rigid senile syndrome in 1.4% and no final diagnosis in 0.7%. The remaining patients (9.8%) had a normal FDOPA uptake pattern, of whom half (50.0%) were finally diagnosed with AD (Table 3). No significant difference was found between mean specific-to-nonspecific ratios in PD versus APS patients (P = NS, Figure 2 and supplemental Figure 1, http://links.lww.com/MD/F154) and between akineto-rigid forms compared with pure tremor in PD patients (P = NS). We observed a higher asymmetry index in PD versus APS ($P = .03$, Fig. 2). Half of patients (55.9%) had a Benamer grade of 1 with a moderate, bilateral and asymmetric striatal impairment (Fig. 1), of whom 82.5% had a final diagnosis of PD, 8.8% of APS, and 0.5% of parkinsonian dementia. Another 33.6% of patients had a Benamer grade 2 and only 0.1% a Benamer grade 3.

3.3. FDG PET/CT

Considering only the results of FDG PET/CT without taking into account the final diagnosis, 58.7% of patients demonstrated a normal uptake pattern or isolated mild hypometabolism of the amygdalo-hippocampal complexes. The remaining 41.3% had a diffuse pattern of cortical hypometabolism involving posterior and/or anterior associative areas, of whom most (61.0%) were finally diagnosed as PD without dementia (Table 3). There was a higher risk of diffuse cortical hypometabolism on FDG PET/CT when patients were diagnosed with APS ($P = .001$, odds ratio = 0.1049 with 95% confidence intervals (CI) [0.0106–0.5295]) rather than PD. A trend for higher risk of diffuse cortical hypometabolism on FDG PET/CT was found in patients with a typical akineto-rigid parkinsonian syndrome compared with those with a pure form of tremor ($P = .06$).

3.4. Impact of dual-tracer PET/CT on final clinical diagnosis

In 112 patients (78.3%), the initial diagnosis suspected by clinicians was confirmed by dual-tracer PET/CT imaging. Interestingly, in 11 patients (7.7%), dual-tracer PET/CT imaging allowed to decide between several diagnostic hypotheses

Table 3

Classification of FDOPA and FDG PET/CT uptake patterns according to the final diagnoses retained by the clinicians after dual-tracer imaging.

	FDOPA		FDG					
Final diagnosis	**Positive**	**Negative**	**0**	**1**	**2**	**3**	**4**	**Totals**
PD	106		5	65	7	4	25	106
APS	10	2		2	3	2	5	12
DLB	*7*	*2*		*1*	*2*	*2*	*4*	*9*
CBD	*1*						*1*	*1*
MSA	*1*			*1*				*1*
PSP	*1*				*1*			*1*
AD		7		2	1	4		7
Parkinsonian dementia	5			3			2	5
Doubt between Parkinsonian dementia or DLB	5			1	1		3	5
Akinetic-rigid senile syndrome	2		1	1				2
Epilepsy		2		1	1			2
Frontotemporal dementia		1					1	1
Essential tremor		1		1				1
No diagnosis	1		1					1
Normal		1	1					1
Totals	129	14	8	76	13	10	36	143

AD = Alzheimer's disease, APS = atypical Parkinsonian syndrome, CBD = cortico-basal degeneration, DLB = dementia with Lewy bodies, MSA = multiple system atrophy, FDOPA = 6-fluoro-(18F)-L-DOPA. FDG = fluorodeoxyglucose. PD = Parkinson's disease. PSP = progressive supranuclear palsy.

(Supplemental Table 1, http://links.lww.com/MD/F152). In the remaining 20 patients (14.0%), dual-tracer PET/CT imaging even led to a new diagnosis that was not initially suspected by clinicians (Supplemental Table 2, http://links.lww.com/MD/F153). Indeed, out of 15 PD initially suspected, 12 (80.0%) had a final diagnosis of DLB (n = 4), parkinsonian dementia (n = 3), or doubt between parkinsonian dementia and DLB (n = 5), while the other 3 patients were diagnosed with an akinetic-rigid senile syndrome (n = 1), early AD (n = 1) and 1 patient was finally considered as normal. Of the 46 patients with an FDG pattern 3 or 4, suggestive of DLB, only 6 were finally retained as DLB by clinicians, while 29 patients were considered PD; only 16 patients had cognitive, memory or executive disorders documented by neuropsychological tests.

3.5. Impact of dual-tracer PET/CT on therapeutic management

No major therapeutic change was observed. In 9 cases (6.3%) of DLB or parkinsonian dementia, in addition to the functional rehabilitation implemented in all patients, a cognitive rehabilitation was also instituted. A new neuropsychological assessment was scheduled. We were unable to gather information on reduction, cessation or introduction of new pharmaceutical classes.

3.6. Disease progression

There was no significant difference in H&Y scores between PD or APS patients (P = NS). Similarly, there was no correlation

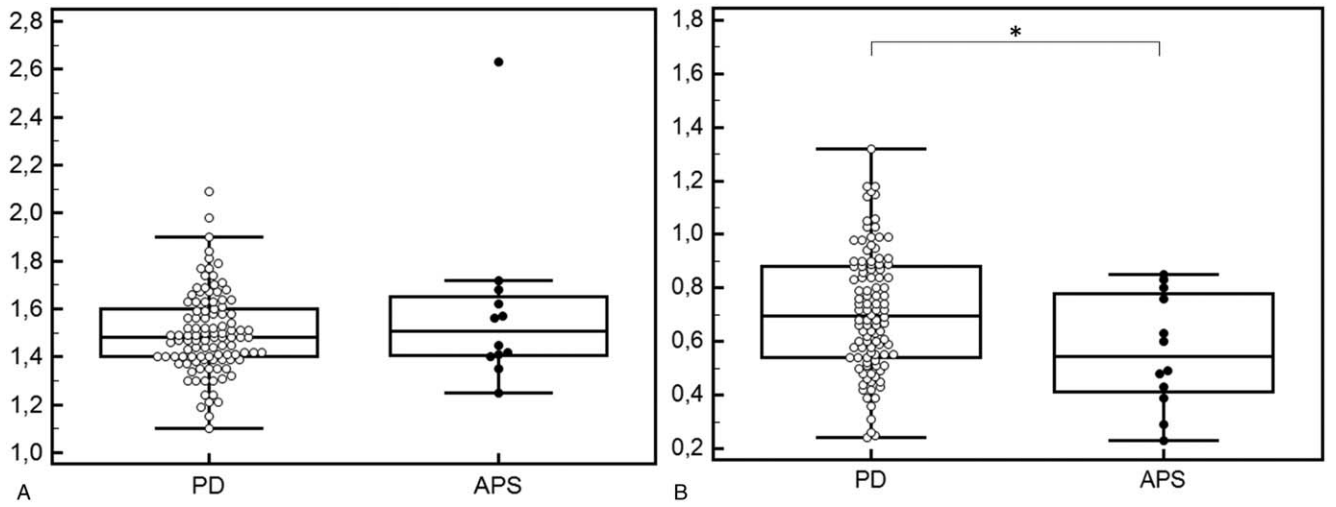

Figure 2. Box plots of mean specific-to-nonspecific uptake ratio (A) and asymmetry index (B) of measured on FDOPA PET/CT in PD and APS. *$P < .05$. APS = atypical parkinsonism syndrome, FDOPA: 6-fluoro-(18F)-L-DOPA, PET/CT = positron emission tomography/computed tomography, PD = Parkinson's disease.

between the H&Y OFF score and the severity of dopaminergic denervation assessed by specific-to-nonspecific uptake ratios in patients with PD or APS (P = NS). No correlation was found between the UPDRS score and the mean specific-to-nonspecific uptake ratio of patients with PD or APS (P = NS). No correlation was found between the mean duration of disease at the time of the first imaging and the mean specific-to-nonspecific uptake ratio in the PD or APS group (P = NS).

4. Discussion

Dual-tracer PET/CT imaging confirmed in 78.3% of cases the initial diagnosis suspected by the clinicians, while in 7.7% of cases, dual-tracer PET/CT was determinant to help the clinicians to retain a final diagnosis between several hypotheses and, in 14% of cases, dual-tracer PET/CT modified the diagnosis initially suspected towards another diagnosis. The major clinical impact of dual-tracer PET/CT was to orient the final diagnosis towards PD, parkinsonian dementia or DLB.

FDOPA PET/CT showed pre-synaptic dopaminergic denervation in 90% of the patients included in this study and was able to rule it out in 10%, mostly AD patients. We observed 2 cases of DLB without pre-synaptic dopaminergic denervation, as already described in the literature and referred to as "cerebral type" of DLB.[10,11] FDOPA PET/CT alone is not considered efficient to differentiate PD from APS patients. In our series, no significant difference was found between specific-to-nonspecific uptake ratios in PD and APS patients, whereas the asymmetry index was significantly higher in PD than in APS patients. Indeed, denervation may be quite symmetrical in some forms of APS.[12,13] FDG PET/CT may help orienting the diagnosis towards APS when a diffuse pattern of hypometabolism is seen. As a fact, we found a higher risk of having diffuse cortical involvement on FDG PET/CT in patients with APS.

Differential diagnosis between DLB and parkinsonian dementia is difficult in clinical practice and specialized neurological tests are needed. Using FDG PET/CT, characterization of these two borderline diseases remains difficult (supplemental Figs. 2–4, http://links.lww.com/MD/F155, http://links.lww.com/MD/F156, http://links.lww.com/MD/F157). A bilateral decrease in FDG metabolism in the occipital, prefrontal and temporo-parietal areas was described in both DLB and parkinsonian dementia patients.[14] Some authors even hypothesized that these two pathologies represent a single entity.[15] However, the severity of executive disorders, the frequency of visual hallucinations and delusions, as well as the relative predominance of postural instability and gait disorders are significantly more important in DLB.[16] In our series, among the 46 cases of suspected DLB on FDG PET/CT, only 6 were retained by clinicians as a DLB, in 2 cases the diagnosis of parkinsonian dementia was retained and in 29 cases a PD; 16 patients had cognitive impairment such as cognitive, memory or executive disorders documented by neuropsychological tests initially performed.

PD patients will eventually evolve towards dementia. A systematic review[17] showed a prevalence of 24% to 31% of dementia in patients with PD. Of the newly-diagnosed patients with PD, 36% had cognitive impairment in the Mini Mental State Examination. On these patients, 57% developed dementia within 3.5 ± 0.7 years.[18] A prospective study[19] showed that there was slight cognitive impairment in 32.9% of newly-diagnosed patients, and therefore, naive to any treatment. Another longitudinal study, including 141 patients with no cognitive impairment at baseline, showed that 47.7% of patients developed a cognitive disorder within 2-6 years and that all developed dementia within 5 y.[20] In non-demented PD patients, a pattern of hypometabolism in posterior temporo-parietal and occipital areas (resembling that of DLB) raises the question whether FDG PET/CT is predictive of cognitive decline in PD.[6] Pilotto et al[21] showed that all patients (n = 13/29) who developed a dementia had an atypical FDG-PET pattern (DLB-like, AD-like, CBD-like, frontotemporal dementia-like, FTD) 4 years before. Cognitive disorders could be detected, in some cases, even before the diagnosis of PD, thus including a risk factor for developing dementia. Diagnostic criteria have been published by the Task Force of the Movement Disorder Society.[22] Rapid Eye Movement (REM) sleep disorders have been identified as prodromal signs of PD.[23] This disorder can be highlighted by a poly-somnographic recording. Hely et al[24] showed a risk 6 times higher to develop dementia when REM sleep disorders are present.

Our study has some limitations and strengths. It is a single centre and retrospective study. We analyzed FDG uptake only with visual interpretation, without standardization like SPM (Statistical Parametric Mapping) because we interpreted scans as in routine practice. However, patients included in this study represent a "real life" cohort and all underwent imaging on the same PET/CT camera with the same acquisition parameters. FDOPA uptake was systematically semi-quantified, allowing correlation with clinical data.

5. Conclusion

Our study shows the usefulness of performing dual-tracer FDOPA and FDG PET/CT for clinical orientation in the evaluation of patients with suspected parkinsonian syndrome associated with cognitive complains. Altogether in this "real life" cohort, dual-tracer imaging was able to guide differential diagnosis or change the diagnosis in 21.7% of patients. A significant prevalence of mild cognitive impairment in PD has been identified on FDG PET/CT and this parameter has been correlated with a higher risk of developing dementia during the disease. It is therefore interesting to perform FDG PET/CT in patients with parkinsonian syndromes and cognitive disorders to optimize the management, with an emphasis on the implementation of cognitive rehabilitation. Further prospective and multicentric studies are needed to clarify this point.

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