Neurobiology of Aging 76 (2019) 9–17

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Neuroimaging findings and clinical trajectories of Lewy body disease in patients with MCI

Federico Massa [a], Dario Arnaldi [a,b], Francesca De Cesari [a], Nicola Girtler [a,c], Andrea Brugnolo [a,c], Matteo Grazzini [a], Matteo Bauckneht [d,e], Riccardo Meli [a], Silvia Morbelli [d,e], Matteo Pardini [a,b], Gianmario Sambuceti [d,e], Fabrizio De Carli [f], Pietro Tiraboschi [g], Flavio Nobili [a,b,*]

[a] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy
[b] Clinica Neurologica, IRCCS Ospedale Policlinico, San Martino, Genoa, Italy
[c] Psicologia Clinica, IRCCS Ospedale Policlinico, San Martino, Genoa, Italy
[d] Department of Health Sciences (DiSSAL), University of Genoa, Genoa, Italy
[e] Medicina Nucleare, IRCCS Ospedale Policlinico, San Martino, Genoa, Italy
[f] Institute of Molecular Bioimaging and Physiology, National Research Council, Genoa, Italy
[g] Division of Neurology V/Neuropathology, Scientific Institute for Research, Hospitalization, and Care (IRCCS), Foundation "Carlo Besta" Neurological Institute, Milan, Italy

ARTICLE INFO

Article history:
Received 23 August 2018
Received in revised form 2 December 2018
Accepted 6 December 2018
Available online 13 December 2018

Keywords:
Lewy body disease
Parkinson's disease
Dementia with Lewy bodies
FDG-PET
DAT-SPECT

ABSTRACT

Elderly patients with mild cognitive impairment (MCI) may develop a Lewy body disease; their neuroimaging features at presentation are largely unknown. We present an intriguing group of 13 patients with MCI preceding (2.9 ± 1.9 years) parkinsonism (MCI-P), and eventually dementia 4.6 ± 1.6 years later (6 patients), whereas 7 patients remained dementia free after 4.7 ± 2.7 years. Neuropsychological tests, dopamine transporter (DAT) single photon emission computed tomography, and ^{18}F-fluorodeoxyglucose positron emission tomography were compared with healthy controls and with cognitively normal patients with Parkinson's disease (PD-MOT). Compared to controls, MCI-P but not PD-MOT showed significant posterior temporo-parieto-occipital hypometabolism. Basal ganglia DAT uptake was similar between MCI-P and PD-MOT. Patients who converted to dementia were older, tended to have higher movement disorder society-unified Parkinson's disease rating scale scores and developed at least another clinical core feature fulfilling the criteria for probable dementia with Lewy bodies (DLB). Concurrent impairment of Corsi span and semantic verbal fluency, or of temporal lobe hypometabolism at baseline and reduced putamen-to-caudate ratio on DAT-SPECT at parkinsonism onset, both predicted ($p < 0.001$) the evolution to dementia. The constructs of Park cognitive subtype and prodromal Lewy body dementia partially overlap; functional imaging and neuropsychology may help in characterizing the patients and in tracking the risk toward dementia.

1. Introduction

Several epidemiological and clinical studies have shown that mild cognitive impairment (MCI) can be detected at the time of Parkinson's disease (PD) diagnosis in a substantial part of patients. The prevalence of MCI varies among studies depending on neuropsychological test batteries and cutoffs used but may be approximated to 25%–30% (Foltynie et al., 2004; Muslimovic et al., 2005; Weintraub et al., 2018). Patients with PD with MCI (PD-MCI) are heterogeneous, presenting with a mixed combination of deficits mainly in executive functions, attention, memory, and visuospatial abilities (Muslimovic et al., 2005). According to the new PD diagnostic criteria, the presence of dementia at parkinsonism onset no longer excludes the diagnosis (Postuma et al., 2015). However, MCI may precede the onset of parkinsonism. Indeed, several epidemiological studies have shown that subtle cognitive deficit could be detected in the years preceding the onset of motor symptoms (Darweesh et al., 2017a,b; Fengler et al., 2017; Pausch et al., 2016; Schrag et al., 2014; Weintraub et al., 2017).

Thus, a patient with underthreshold motor symptoms due to an alpha-synucleinopathy may come to neurological attention

* Corresponding author at: Deparment of Neuroscience (DINOGMI), University of Genoa Clinica Neurologica, IRCCS Ospedale Policlinico, San Martino, Genoa, Italy. Tel.: +39 0103537568; fax: +39 0105556893.
E-mail address: flaviomariano.nobili@hsanmartino.it (F. Nobili).

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https://doi.org/10.1016/j.neurobiolaging.2018.12.001

complaining about a decline in cognitive performances, without presenting clear clinical evidence of motor difficulties. If objective cognitive impairment is demonstrated, such a patient would be labeled as affected by MCI and may be followed by a memory clinic instead of a movement disorder unit. When parkinsonism would be evident, the label would become PD-MCI (but with the peculiarity that cognitive deficit precedes motor symptoms), and eventually PD dementia (PDD) if in the course of time he or she losses autonomy in everyday life.

This construct is increasingly recognized but also overlaps another construct, that of dementia with Lewy bodies (DLB) in its prodromal (or MCI) stage (Fujishiro et al., 2015). Although shared criteria for the diagnosis of prodromal DLB have not been published yet, the 2017 DLB Consortium criteria acknowledged that they are under discussion (McKeith et al., 2017). Noteworthy, plenty of nonmotor and noncognitive symptoms typical of alpha-synucleinopathies are common to the 2 entities, ranging from rapid eye movements sleep behavior disorders (RBD) to hyposmia and constipation.

Thus, there is no agreement yet on how to label a patient with MCI who later develops parkinsonism and eventually dementia. Even the diagnosis of DLB does not rule out the diagnosis of PD according to the new PD criteria (Postuma et al., 2015). The debated 1-year rule (Boeve et al., 2016; Postuma et al., 2016) would define such a patient as affected by DLB if dementia precedes parkinsonism, or if parkinsonism comes first, within 1 year prior of dementia onset. However, if MCI precedes parkinsonism for a longer time, this patient remains essentially undefined.

Recently, the concept of “prodromal” Lewy body disease (LBD) has been proposed (Donaghy and McKeith, 2014) considering PD and DLB being 2 extremes of the same LBD spectrum (Berg et al., 2014). It has been suggested that at this very early LBD stage, it might not be possible to predict which phenotypic pathway the patient will subsequently follow (McKeith et al., 2016). However, biomarker investigation and strict clinical follow-up may subsequently clarify his or her position along the axis with PD and DLB at the 2 extremes (McKeith et al., 2016).

In the attempt to characterize the neuroimaging and neuropsychological characteristics of this intriguing category of patients, we present a group from our outpatient clinics dedicated to brain neurodegenerative conditions who presented with a heterogeneous MCI condition, then developing parkinsonism and receiving a diagnosis of PD, and eventually (half of them) converting to dementia in the short-to-medium term follow-up. Neuroimaging includes brain magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) acquired at baseline, and dopamine transporter single photon emission computed tomography (DAT-SPECT) acquired at the time of PD diagnosis.

2. Materials and methods

2.1. Patients

This is a case series of 13 patients (Table 1) who came to our outpatient neurological unit for neurodegenerative diseases between October 2004 and March 2017 because of cognitive complaints. This group has been extracted from a cohort of 567 patients who were diagnosed as affected by MCI from different etiologies in the same period (363 were diagnosed as affected by MCI due to AD) when 91 patients were diagnosed as de novo PD.

2.1.1. Baseline assessment

At the time of their first diagnostic workup (baseline), patients underwent neurological evaluation, an extended neuropsychological test battery (supplementary material), and brain MRI. All patients presented an impairment in 2 or more neuropsychological tests but had preserved activities of daily living (ADL) and instrumental ADL (IADL) based on both clinical interview and formal questionnaires. Clinical dementia rating scale was 0.5 in all patients, fitting the criteria for MCI.

Table 1
Main baseline demographic and clinical features of 13 patients with MCI-P

Patient N°	Age (yrs)	Gender	Education (yrs)	MMSE score	GDS-15 score
1[a]	75.7	M	13	26	5
2	69.5	M	8	27	0
3	79.8	F	13	29	9
4[a]	80.7	M	8	27	2
5[a]	78.2	M	12	26	5
6[a]	70.0	F	5	27	3
7	75.4	M	5	29	2
8	75.3	M	5	21	7
9	74.6	M	17	29	4
10	69.6	F	3	29	1
11[a]	78.2	F	10	30	4
12[a]	73.9	M	13	24	0
13	72.0	M	21	28	1
Mean	74.8	9M	10.3	27.1	3.3
SD	3.8	4F	5.3	2.5	2.7

Key: SD, standard deviation; F, female; M, male; MMSE, mini mental state examination; GDS-15, 15-item geriatric depression scale.
[a] Patients later converted to dementia.

Eleven patients also underwent FDG-PET with the aim of clarifying the underlying cause of cognitive deficit. Five patients (Table 1: no 1, 5, 6, 9, 12) were tentatively labeled as MCI because of AD, according to clinical-neuropsychological profiles and neuroimaging (MRI and FDG-PET) findings (Fig. 1) but acknowledging an intermediate likelihood. Further confirmation was unfeasible as biomarkers of amyloidosis were unavailable at our center in those years. The remaining 8 patients were labeled as MCI of unknown origin.

2.1.2. Assessment at PD diagnosis

Patients were then regularly followed-up every 6–12 months with clinical evaluation. During the follow-up period, 9 patients were administered selective-serotonin uptake inhibitors or selective-norepinephrine uptake inhibitors, and 2 received low-dose bedtime benzodiazepines.

After a mean time of 2.9 $\pm$ 1.9 years (range 0.5–6.1), all patients developed motor symptoms fitting the diagnostic criteria for PD in use at the time when the diagnosis was made (Gelb et al., 1999) (Table 2). Dopamine neuronal degeneration as a cause of parkinsonism, further supporting clinical PD diagnosis, was confirmed by means of DAT-SPECT in all instances (PD diagnosis) (Fig. 1). As PD was diagnosed after MCI, we tentatively named these patients as MCI-P instead of PD-MCI, in whom MCI follows the PD diagnosis. Moreover, the same clinical-neuropsychological assessment administered at baseline was repeated at the time of PD diagnosis in 10 patients.

At this time, patients were further investigated to assess the presence of both motor and nonmotor symptoms of PD (Table 3). Beyond the movement disorder society-unified Parkinson's disease rating scale (MDS-UPDRS) and the Hoehn and Yahr (H and Y) scales, this included (1) automatic blood pressure measurements in the supine position and after 3 minutes of standing (orthostatic hypotension was defined as a systolic blood pressure drop $\geq$20 mm Hg and/or a diastolic blood pressure drop $\geq$10 mm Hg during standing); (2) investigation of the presence/absence of constipation, urinary, and sexual dysfunction with the clinical interview; (3) olfaction by means of the Smell diskettes olfaction test (Briner and Simmen, 1999); hyposmia was defined with more than 1 mistake;

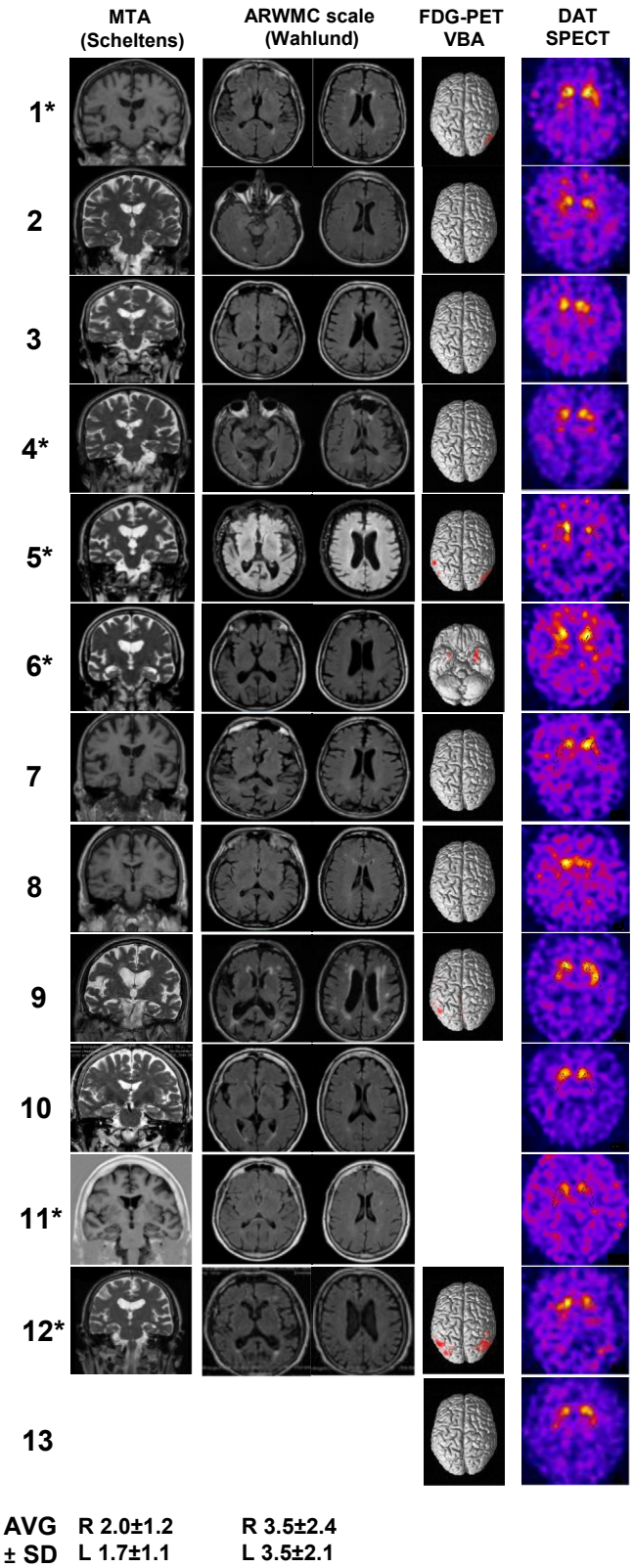

Fig. 1. Coronal MR images are shown on the left, transaxial MR images in the middle, followed by results of voxel-based statistical comparison of individual FDG-PET with normal controls (SPM tool), and by a sample image of DAT-SPECT on the right. Individual FDG-PET and DAT-SPECT images are shown without flipping hemispheres according to the most affected side (see Section 2.4.2 for further details). Scheltens' MTA scale was applied to T2-weighted images in patients 2, 3, 4, 5, 6, 9, 10, 12, to T1-weighted images in patient 1, T1-MPR–weighted images in patient 7, 8 and to T1-IR–weighted images in patient 11. For ARWMC scale, T2-Flair–weighted images were used, except for patient 5 for which only a T2 Flair-Spir–weighted image was available. Patient 13 underwent CT because of contraindication to MRI. In patient 4, a frontal hypodense area is a result of trauma in the young age. Patient 10 underwent perfusion single photon emission tomography instead of FDG-PET. *, patients later converted to dementia. Abbreviations: ARWMC, age-related white matter changes; Flair, fluid attenuation inversion recovery; IR, inversion recovery; L, left hemisphere; MTA, medial temporal atrophy; MRP, multiplanar reconstruction; R, right hemisphere; Spir, spectral presaturation with inversion recovery.

and (4) the Mayo sleep questionnaire (Boeve et al., 2011) and a semistructured clinical interview (Scaglione et al., 2005) by a sleep medicine expert (D. A.) to investigate the presence/absence of probable RBD that was dichotomously detected based on the first question of the questionnaire and confirmed by the clinical interview.

2.1.3. Assessment at follow-up

The 13 patients started dopaminergic treatment according to the clinical needs. Moreover, other drugs including selective-serotonin uptake inhibitors and selective-norepinephrine uptake inhibitors were used based on clinical judgment. They were then periodically assessed for a further mean follow-up time of 2.1 ± 2.0 years (range 0.5–6.3 years) with administration of the mini mental state examination (MMSE) and the clinical dementia rating scale, ADL, and IADL scales. Mean time from baseline to last available evaluation was 5.0 ± 2.2 years (range 2.4–9.1).

2.2. Control groups

Two control groups were set up with a case-control criterion. The first one (PD-MOT) was represented by 11 de novo patients with PD without cognitive complaints or impairment (MMSE score >27; no impairment on neuropsychological tests), selected from our database in the same period so as to be similar for sex (M:F = 8:3), age (74.9 ± 5 years; range 67.7–82.9 years), education (10.36 ± 4.74 years; range 5–17 years), and MDS-UPDRS III score (20.9 ± 10.52; range 10–46) with patients with MCI-P. All PD-MOT patients underwent the same diagnostic battery as patients with MCI-P (i.e. neuropsychological evaluation, brain MRI, FDG-PET, and DAT-SPECT). Also, they were followed-up (mean time 27.1 ± 16.6 months, range 9–66) with the same rules as for patients with MCI-P. At the last follow-up visit, no patient in PD-MOT group had MCI or dementia (mean MMSE score: 29.3 ± 0.47).

The second group included 18 healthy controls (HC), matched for sex (14 males, 4 females), age (75.9 ± 4.5 years; range 70.1–84.3 years), and education (11 ± 4.31 years; range 5–17 years) with MCI-P patients, who had undergone FDG-PET in the frame of a previous study (Morbelli et al., 2012).

Both patients and controls gave consent to use anonymized data according to the declaration of Helsinki.

2.3. Neuroimaging

Brain MRI was performed by means of different 1.5 Tesla equipments, using standard sequences in most cases because it was a diagnostic exam performed for clinical purposes. One patient (no. 13) underwent computed tomography because of claustrophobia.

FDG-PET was performed according to the European Association of Nuclear Medicine (EANM) guidelines (Varrone et al., 2009) in 11 patients. One more patient (no. 10) underwent perfusion single photon computed tomography with ^{99m}Tc-HMPAO.

DAT-SPECT was obtained after i.v. administration of about 185 MBq of ^{123}I-Ioflupane (DaTSCAN) in all patients, basing on the EANM guidelines (Darcourt et al., 2010).

Table 2
Main clinical features of 13 patients with MCI-P at the time of PD diagnosis

Patient n°	Time baseline-PD diagnosis (yrs)	More affected body side	Main clinical signs/symptoms	MDS-UPDRS –III score	H and Y score
1[a]	2.0	R	Resting tremor, mild rigidity UL	14	1
2	4.5	R	Mild rigidity	8	1
3	1.0	L	Mild axial rigidity	12	2
4[a]	1.6	L	Mild limb rigidity, bilateral resting tremor	19	2
5[a]	3.5	R	Diffuse rigidity	45	2
6[a]	5.6	L	Left UL resting tremor, axial rigidity	36	2
7	3.2	R	Resting tremor right limbs, mild rigidity	30	1
8	1.7	R	Right arm resting tremor	25	2
9	0.5	L	Pisa Syndrome, mild	11	2
10	4.9	R	Right arm resting tremor	20	3
11[a]	1.1	R	Axial rigidity	9	2
12[a]	6.1	R	Axial rigidity	38	2
13	2.2	R	Mild UL rigidity	10	2
Mean	2.9			21.3	1.8
SD	1.9			12.4	0.5

Key: SD, standard deviation; F, female; M, male; H and Y, Hoehn and Yahr scale; L, left; R, right; MDS-UPDRS-III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor section; UL, upper limb; Y, yes.
[a] Patients later converted to dementia.

Details of acquisition, reconstruction, and post-processing are in Supplementary Materials.

2.4. Statistical analysis

2.4.1. Neuropsychological tests

Individual neuropsychological test scores in the 13 patients with MCI-P (both at baseline and diagnosis) and in patients with PD-MOT were compared with normal reference values in local language, correcting for age and education (Capitani and Laiacona, 2000; Spinnler and Tognoni, 1987; Vallar and Papagno, 2007). Neuropsychological test scores in MCI-P group at baseline were compared with the corresponding test scores in PD-MOT group and with those at the time of PD diagnosis (*t*-test, false discovery rate-corrected for multiple comparisons).

2.4.2. Neuroimaging

Before submitting both FDG-PET and DAT-SPECT images to statistical analysis between groups, we flipped images so as to place in the same side the more affected hemisphere, defined as the contralateral side to the more affected side of the body, a procedure already largely used in neuroimaging studies in patients with PD (Arnaldi et al., 2017; Nobili et al., 2010; Tang et al., 2010).

At individual level, DAT-SPECT was examined by an expert nuclear medicine physician (S. M.) who rated the scan as abnormal in all patients. Moreover, specific-binding ratio (SBR) values at putamen and caudate level were compared with the control population embedded within the Basal Ganglia V2 software (Calvini et al., 2007) and were significantly below the normal threshold in at least 1 nucleus in all patients. At group level, SBRs were compared between the MCI-P and PD-MOT groups (*t*-test).

At group level, Statistical Parametric Mapping-version 12 ([SPM12]; unpaired *t*-test) was used to compare FDG-PET between MCI-P group and each of the 2 control groups, namely HC and PD-MOT, respectively. Moreover, MCI-P and PD-MOT groups were directly compared to each other. At individual level, brain metabolism in each patient with MCI-P was compared to the healthy control group to obtain individual maps of relative hypometabolism, as recently used in patients with PD (Pilotto et al., 2018).

2.4.3. Comparison between converters and nonconverters to dementia

Demographic and main clinical characteristics between converters and nonconverters were compared by means of *t*-test. The global cognitive changes in converters and nonconverters were expressed by the MMSE score at 3 time points, that is, baseline, PD diagnosis, and follow-up and explored by means of ANOVA for repeated measures.

Table 3
Timing of onset of non motor symptoms and L-DOPA response in 13 patients with MCI-P

Pt no	Hyposmia		Constipation		Urinary incontinence		OH		Probable RBD		VH	AF	L-DOPA response
	PD-d	FU	PD-d	FU	PD-d	FU	PD-d	FU	PD-d	FU	FU	FU	FU
1[a]									Y				
2	Y		Y						Y		Y	Y	
3	Y		Y					Y	Y				Y
4[a]	Y										Y		
5[a]	Y		Y						Y		Y	Y	
6[a]			Y						Y				Y
7	Y		Y										Y
8	Y								Y				Y
9			Y										Y
10	Y		Y		Y		Y						Y
11[a]					Y						Y[b]		Y
12[a]			Y		Y					Y	Y	Y	Y
13	Y												Y

Key: PD-d, time of PD diagnosis; FU, follow-up; OH, orthostatic hypotension; VH, visual hallucinations; AF, attention fluctuations; RBD, probable REM sleep behavior disorder; Y, yes.
[a] Patients later converted to dementia.
[b] Auditory hallucinations.

We then explored whether FDG-PET, MRI visual assessment, and neuropsychological test scores at baseline as well as DAT-SPECT at the time of PD diagnosis could predict conversion. Taking into account the small sample size and the consequent risk of overfitting, we applied a preliminary univariate group comparison (*t*-test) between the 2 subgroups to select the most promising ($p < 0.1$) predictors for this explorative analysis. In this way we identified the right MTL atrophy Scheltens' score for MRI ($p = 0.025$), the metabolic levels in the left temporal pole ($p = 0.042$) and in the average of the 2 temporal lobes ($p = 0.069$) for FDG-PET, the Corsi span ($p = 0.024$) and the categorical semantic verbal fluency test ($p = 0.054$) among the neuropsychological tests, and the ratio between Putamen and Caudate SBRs in the less affected hemisphere (LAH) ($p = 0.062$) for the DAT-SPECT. As for FDG-PET, uptake values were considered in 26 meta-VROI as described elsewhere (Pagani et al., 2017) and normalized to whole brain counts.

Then, in a second step, a logistic regression linear model was applied including these variables as predictors. Conversion to dementia was the binary outcome with expected binomial distribution. Further details on statistical analysis are described in Supplementary Material.

3. Results

3.1. Neuropsychological evaluation

At baseline, MCI presentation was very heterogeneous. Seven patients (no 1, 2, 5, 6, 7, 8, 12) had multidomain amnesic MCI with concomitant deficit in executive functions (6 patients), language (3 patients), and visuoconstruction (3 patients). Two patients (no. 9 and 10) had multidomain nonamnesic MCI, mixing deficit in executive functions (both) with language or visuoconstruction (one each). The remaining 4 patients had either single-domain nonamnesic (dys-executive) (no. 3, 4, 13) or amnesic (no 11) MCI.

The clock drawing was the most frequently impaired test (7 patients), followed by the TMT-B and the RAVLT, immediate recall (5 patients each). Table 4 reports the results of neuropsychological test comparison between MCI-P group at baseline and PD-MOT group.

At PD diagnosis (evaluation available in 10 patients), several test scores worsened at individual level. At group level, the comparison between the neuropsychological tests at baseline and at PD diagnosis showed worsening in several test scores, however not surviving false discovery rate correction for multiple comparisons (Supplementary Table 1).

3.2. Magnetic resonance imaging

Individual neuroimaging findings at baseline are shown in Fig. 1. Briefly, significant MTL atrophy (i.e. scoring >2 on Scheltens' scale in at least one side) was found in pts. 1, 5, 6, and 9, whereas moderate to severe charge of white matter hyperintensities was found in pt. 1 and 9. The Scheltens' scale for MTL atrophy scored 2.0 ± 1.2 in the right hemisphere and 1.7 ± 1.1 in the left one, whereas the age-related white matter changes scale for white matter hyperintensities scored 3.5 ± 2.4 in right hemisphere and 3.5 ± 2.1 in the left one. Individual voxel-based MRI analysis was unfeasible because of the different acquisition protocols and equipments that were used in the clinical setting, as the patients performed MRI on their own at different sites.

3.3. DAT-SPECT

No significant difference was found for SBRs in each of the 4 basal ganglia between the group of patients with MCI-P and PD-MOT group (Table 4).

Table 4
Comparison between neuropsychological test scores at baseline and SBRs of DAT-SPECT at the time of PD diagnosis between MCI-P and PD-MOT groups

	Baseline		
	MCI-P	PD-MOT	p[a]
MMSE	27.1 ± 2.5	28.8 ± 1.2	**0.04**
Corsi span	4.0 ± 0.6	4.5 ± 0.5	**0.04**
Digit span	5.4 ± 0.8	5.4 ± 0.8	n.s.
Babcock story recall	8.4 ± 3.6	12.1 ± 3.6	**0.03**
RAVLT immediate	28.1 ± 10.7	34.2 ± 6.8	n.s.
RAVLT delayed	4.5 ± 2.6	6.1 ± 1.7	n.s.
Trail Making Test A	89.7 ± 38.3	55.7 ± 15.3	**0.02**
Trail Making Test B	453.1 ± 263.0	133.2 ± 65.7	**0.003**
Digit symbol	18.4 ± 8.6	30.0 ± 9.0	**0.01**
Stroop color	30.1 ± 5.8	37.3 ± 5.4	**0.01**
Stroop color word	8.0 ± 3.3	15.2 ± 4.6	**0.003**
Clock drawing	4.4 ± 4.1	5.9 ± 6.7	n.s.
Figure simple copy	8.1 ± 1.7	9.7 ± 1.0	**0.02**
Figure copy with guiding landmarks	64.0 ± 4.7	66.9 ± 3.1	n.s.
Semantic verbal fluency	25.2 ± 7.0	33.6 ± 13.8	n.s.
Phonological verbal fluency	24.0 ± 12.9	29.1 ± 8.9	n.s.
Caudate SBR (MAH)	2.5 ± 0.8	2.7 ± 0.4	n.s.
Caudate SBR (LAH)	2.7 ± 0.7	2.9 ± 0.5	n.s.
Putamen SBR (MAH)	1.0 ± 0.6	1.0 ± 0.4	n.s.
Putamen SBR (LAH)	1.2 ± 0.6	1.2 ± 0.4	n.s.

Mean vales and standard deviation values are shown.
Bolded values represents the comparisons reaching statistical significance.
Key: MMSE, mini mental state examination; PD, Parkinson's disease; MAH, more affected hemisphere; LAH, less affected hemisphere; RAVLT, Rey Auditory Verbal Learning Test; SBR, specific binding ratio.
[a] False discovery rate-corrected for multiple comparisons.

3.4. FDG-PET

Areas of significant hypometabolism were found in posterior parieto-occipital association cortex in pts no. 1, 5, 9, 12, whereas pt. 6 disclosed medial temporal lobe hypometabolism; the other patients did not show significant hypometabolic clusters (Fig. 1). Thus, 4 among the 5 patients converting to dementia in whom FDG-PET was available (missing in pt no. 11) exhibited significant hypometabolism already at baseline examination, 4.6 years in advance (in average), versus only 1/6 nonconverters.

At group level compared to HC group patients with MCI-P showed significant hypometabolism in bilateral middle temporal gyrus (Brodmann area 39, BA39), superior and middle occipital gyrus (BA19) and precuneus (BA7) in the left hemisphere, supramarginal gyrus and inferior parietal lobule (BA40) in the right one (Fig. 2). Supplementary Table 2 reports the Talairach coordinates and BAs of clusters of significant hypometabolism.

No significant cluster of hypometabolism was found in PD-MOT compared to HC, as well as in the direct comparison between MCI-P and PD-MOT groups.

3.5. Clinical follow-up and subgroup analyses

Following the diagnosis of PD, all but 4 patients (Table 3) showed a fair to good motor response to dopaminergic treatment, whereas 3 patients (no 9, 11, 13) showed also some cognitive improvement. Six patients (highlighted with asterisk in Tables 1–3) converted to dementia after a mean of 4.6 ± 1.6 years (range 2.8–6.4 years) from baseline and 1.3 ± 1.1 years (range 0.5–2.9 years) from PD diagnosis (converters), whereas 4 of them converted within 1 year after PD diagnosis, 2 (no. 4, 11) converted 1.9 and 2.9 years later, respectively. Instead, 7 patients remained at an MCI stage (nonconverters; mean follow-up time from baseline: 4.8 ± 2.6 years). During the follow-up period, hallucinations were reported in 4/6 among converters but only in 1/7 among nonconverters, attention fluctuations in 2 converters and 1 nonconverter, RBD in 1 converter, and orthostatic

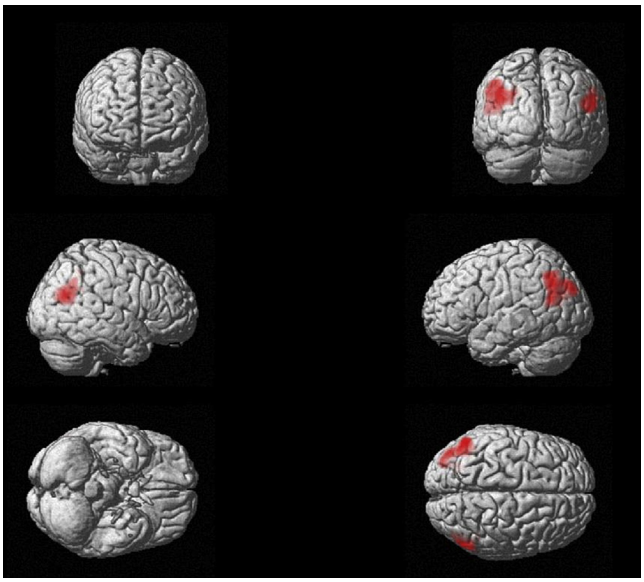

Fig. 2. Results of SPM-12 comparison (uncorrected $p < 0.001$ at voxel level) between the group of 13 MCI-P patients and HC. Areas of significant ($p < 0.05$ family-wise corrected for multiple comparisons at cluster level) relative hypometabolism are shown in red, superimposed onto a brain rendering. Significant clusters ($p < 0.0001$ in the left hemisphere, $p < 0.001$ in the right one) of hypometabolism in MCI-P group was found in bilateral middle temporal gyrus (BA39), supramarginal gyrus and inferior parietal lobule (BA40) in the right hemisphere, and in superior and middle occipital gyrus (BA19) and precuneus (BA7) in the left hemisphere. Details of coordinates in Supplementary Table 2. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

hypotension in a nonconverter, whereas hyposmia was less represented in converters than in nonconverters.

As compared to nonconverters, converter patients were older (77.3 ± 2.61 vs 73.7 ± 3.7; $p < 0.05$), were more often affected by amnestic MCI (5/6 instances vs. 3/7 in nonconverters), and tended to have a higher MDS-UPDRS-III score (26.8 ± 14.7 vs 16.6 ± 8.5; $p = 0.07$). The H and Y scale score, time from baseline to PD diagnosis, and other features were similar between the 2 subgroups. Also, there was no significant difference in the time lasted from the baseline visit to PD diagnosis between nonconverters (2.6 ± 1.8 years) and converters (3.3 ± 2.1 years). In nonconverters patients, the MMSE scored was 27.4 ± 2.9 at baseline, 28.0 ± 1.5 at PD diagnosis, and 26.6 ± 1.5 at follow-up. In converter patients, the MMSE scored was 26.5 ± 1.8 at baseline, 25.8 ± 2.0 at PD diagnosis, and 20.7 ± 1.8 at conversion time. Data were analyzed by means of ANOVA for repeated measures with MMSE score as the dependent variable, group as the between-factor variable, and time as the within factor variable. ANOVA showed a significant effect both of time ($p < 0.001$) and group ($p = 0.002$) with a significant of time*group interaction ($p < 0.01$) (Supplemental Figure).

The stepwise logistic regression analysis performed on selected baseline neuroimaging, and neuropsychological variables and on DAT-SPECT at time of PD diagnosis identified the Corsi span and the categorical semantic verbal fluency tests as best predictors, fully separating converters from nonconverters ($p < 0.001$). The analysis was then repeated including only neuroimaging variables (to exclude those variables directly measuring cognitive performances and thus more intuitively predicting conversion to dementia). The model including the ratio between Putamen and Caudate SBRs in the LAH and the average of metabolic levels in the 2 temporal lobes on FDG-PET allowed a complete separation between the 2 subgroups ($p < 0.001$) (see Supplementary Table 3 for mean values and SDs).

4. Discussion

This case series shows that an elderly patient with PD may initially ask for neurological consultation because of cognitive rather than motor symptoms. The latter can develop later during the course of the disease or, alternatively, they may initially be so subtle as to be hardly identifiable. Our patients could be labeled as having prodromal DLB (McKeith et al., 2017), MCI-subtype (McKeith et al., 2016) but, according to what is implicitly stated in the new MDS PD criteria (Postuma et al., 2015), they might also be labeled as patients with PD with a cognitive presentation. However, the distinction between prodromal DLB and PD with a cognitive presentation seems blurry at the pathophysiological level, and these patients might be labeled as affected with prodromal LBD, as suggested by some authors (Donaghy and McKeith, 2014; McKeith et al., 2016). In fact, they all exhibited parkinsonian motor symptoms, MCI, nigrostriatal deafferentation on DAT-SPECT, and a combination of nonmotor symptoms typical of alpha-synucleinopathies.

Our patients with MCI-P were rather old at baseline (almost 75 years in average) thus more in the range of DLB (Savica et al., 2013) than of PD age of onset. However, the age at diagnosis observed in our study is similar to the mean age of the so called “Park cognitive subtype” (Halliday et al., 2011; Sauerbier et al., 2016). As compared to “pure” motor-onset (i.e., with normal cognition) PD of same age, they disclosed similar severity of nigrostriatal impairment but more severe hypometabolism in bilateral temporo-parietal association cortex and in left occipital cortex, in keeping with findings in patients with PD-MCI (Bohnen et al., 2011; Firbank et al., 2017; Pappatà et al., 2011; Shoji et al., 2014; Tard et al., 2015). Taken together, the study evidence suggests a prominent hypometabolism in posterior temporal and parietal cortex as well as in lateral association occipital cortex in patients with PD with MCI and some discrepancies among studies more likely derive from the limited number of patients included in each study.

Instead, brain metabolism did not differ between HC and PD-MOT groups. FDG-PET has been extensively investigated in PD, and a characteristic PD-related pattern has been described already in the less affected hemisphere in de novo PD (Tang et al., 2010) and in patients with idiopathic RBD as well (Holtbernd et al., 2014; Meles et al., 2018). Moreover, a PD cognitive-related metabolic pattern has been described (Huang et al., 2008), overlapping the parietal clusters of hypometabolism we found in our patients and highlighting also lateral prefrontal cortex hypometabolism. Furthermore, Firbank et al. (2017) reported glucose hypometabolism in bilateral posterior temporo-parietal cortex to characterize de novo patients with PD-MCI, in similar regions as in our patients. They also found occipital hypometabolism both in patients with PD-MCI and PD without cognitive impairment. Occipital hypometabolism has been repeatedly reported in PD (Bohnen et al., 2011; Garcia-Garcia et al., 2012; González-Redondo et al., 2014) as well as in DLB where it was mainly unrelated to cognitive impairment (Meyer et al., 2014). Although we found left occipital hypometabolism in MCI-P, we failed to find it in PD-MOT but it should be remarked that our patients with PD-MOT were specifically selected so as to be devoid of cognitive impairment on an extended neuropsychological test battery and they all remained cognitively normal at follow-up. Instead, our failure to observe significant metabolic differences in the direct comparison between MCI-P and PD-MOT groups could be because of the small group size, as happened in other studies (Pappatà et al., 2011). The novelty of our finding is the demonstration of posterior temporo-parieto-occipital hypometabolism more than 2 years before the onset of motor symptoms in MCI-P group, a finding that is not evident in patients

with PD without significant cognitive impairment. In this context, FDG-PET confirms its sensitivity to correlate with cognitive symptoms, as in MCI due to AD (Shokouhi et al., 2013).

During the follow-up lasting about 5 years in average, roughly half of our patients with MCI-P developed dementia. Overall, those converting to dementia were older, tended to have a worse MDS-UPDRS-III score, were more frequently affected by amnesic than nonamnesic MCI, and showed some peculiarities in neuroimaging. In some instances, the MDS-UPDRS III score increase was remarkably high. This could be explained by the relatively long time between visits (until 1 year in some cases) and by the possible rapid worsening of motor symptoms in patients with DLB as compared to patients with PD (Burn et al., 2006). At individual level, MTL atrophy was more frequent in converters than in nonconverters, whereas white matter damage was similar. This is in keeping with other MRI studies showing more severe MTL atrophy in patients with PD converting to dementia in the short-to-medium term (Chen et al., 2017; Ibarretxe-Bilbao et al., 2011). Moreover, patients converting to dementia also exhibited more often clusters of hypometabolism in posterior parieto-occipital association cortex than in nonconverters.

When we grouped patients into converters and nonconverters to dementia, we found that a worse performance on working memory and semantic verbal fluency at baseline fully separated converters from nonconverters. Also, we found that a lower putamen-to-caudate SBR ratio in the LAH on DAT-SPECT at the time of PD diagnosis associated with temporal lobe hypometabolism gave the same result, whereas MTL atrophy score did not reach the statistical significance. Semantic verbal fluency has been recently reported as 1 of the most significant predictors of DLB in a cohort of patients with idiopathic RBD (Marchand et al., 2018), and our results support its role in this direction. Semantic verbal fluency directly involves temporal lobe function, mainly in the left hemisphere, and indeed we found average baseline temporal lobe hypometabolism among predictors of conversion. Actually temporal lobe hypometabolism is part of the hypometabolic pattern in DLB already at the prodromal stage (Huang et al., 2015). Interestingly, the inferior temporal gyrus and the precuneus were the sites of highest uptake of the [18F]AV-1451 Tau PET tracer in patients with DLB (Gomperts et al., 2016). Moreover, patients with DLB were shown to carry higher Lewy bodies' burden especially in the temporal and parietal lobes as compared to both patients with PD and PDD in a large neuropathological series (Ruffmann et al., 2016). On the other hand, a lower putamen-to-caudate SBR ratio in converters reflects the trend to a more severe motor impairment; we found in converters and point to a worse course of dopaminergic neurodegeneration than in nonconverters, in keeping with previous data showing a worse nigrostriatal function in patients with DLB than in PD (Ransmayr et al., 2001).

The presence of MTL atrophy and/or posterior hypometabolic pattern together with an amnesic MCI syndrome led us at first evaluation to the wrong hypothesis of MCI because of AD in 5 patients (4 belonging to those subsequently developing dementia) until motor symptoms manifested about 3 years later, whereas the remaining 8 were labeled as MCI of unknown origin. Of paramount importance, we were wrong at baseline evaluation because in those years we missed to investigate crucial symptoms, such as the presence of probable RBD and hyposmia, which were searched for only at the time of PD diagnosis. Indeed, these symptoms often precede the diagnosis by years and they were likely already present at baseline in most patients. Thus, a lesson we have learnt from this clinical experience is that nonmotor symptoms of synucleinopathies should be carefully checked in all patients presenting to a memory clinic complaining of cognitive deficit and then confirmed to be affected with MCI.

Therefore, the trajectories we observed in our patients with MCI-P seem to identify on the one hand what it may be labeled "prodromal DLB" at least for 4 of the 6 patients developing dementia (in 2 patients dementia developed more than 1 year later and thus they should formally more properly labeled as PDD patients, according to the 1-year rule), and on the other hand "PD with cognitive onset" (or Park cognitive subtype) for the other 7. In the former subgroup, the development of dementia after MCI and parkinsonism is also accompanied by the onset of at least one other core symptom of DLB during the follow-up and is supported by an indicative biomarker (DAT-SPECT) according to the 2017 DLB criteria (McKeith et al., 2017), thus the criteria for DLB preceded by a prodromal stage should be fully satisfied, at least in 4 of them. Looking instead at the period between baseline and PD diagnosis, there were no time differences between converters and nonconverters.

We lacked amyloidosis biomarkers but brain amyloidosis may be present in patients with DLB, PDD, and even PD without dementia (Akhtar et al., 2017; Petrou et al., 2015), thus knowing the amyloid state would have been of little help in identifying the correct diagnosis. Moreover, the prevalence of incidental amyloidosis increases dramatically after the age of 75 years, especially in ApoE4 positive subjects (Ossenkoppele et al., 2015), and about half of our patients were indeed older than 75.

In 4 of the 7 patients not developing dementia, a second core symptom was missing to fulfill the DLB criteria. Because they did not become demented after almost 5 years, it is unlikely they suffer from prodromal DLB, unless we admit a very long incubation stage because the onset of MCI, thus they may more properly be labeled as "Park cognitive subtype" but with a cognitive onset. Of note, all but one showed good response to L-DOPA treatment, which may further support this interpretation (Sauerbier et al., 2016). As about 25%–30% of patients with PD show MCI already at the time of diagnosis (Foltynie et al., 2004; Muslimovic et al., 2005), one may wonder why such a patient could not ask for neurological consultation because of cognitive symptoms some time before the motor symptoms appear. Cognitive deficits, especially in speed processing and executive functions, are detectable even 7 years before diagnosis, whereas memory complaints are actually reported less than 2 years before PD diagnosis (Darweesh et al., 2017a; Postuma et al., 2015). The concept of "Park cognitive subtype" in which both cortical neurodegeneration and Lewy bodies deposition are prominent in early stages, presenting as early MCI has been proposed by the King's college group (Sauerbier et al., 2016). According to those authors, these patients could represent the late-onset pattern of Lewy body deposition (Halliday et al., 2011), overlapping clinically with DLB and even AD.

An obvious limitation of the study is the small number of patients. Such a small sample size, however, is not surprising since, as compared to subjects with MCI concomitant or following PD onset, those with MCI preceding PD are considerably fewer. Another limitation is given by the relative heterogeneity of the MR images stemming from the retrospective nature of the study.

In conclusion, in this small series, we have intercepted 2 different trajectories after 5 years of follow-up since the first presentation of cognitive complaints. Older age, presence of at least another DLB core feature beyond parkinsonism, a worse working memory and semantic verbal fluency, or signs of more severe neurodegeneration on FDG-PET and DAT-SPECT characterized the evolution to dementia with the DLB features. We conclude that the only realistic diagnostic label at the very first presentation of symptoms would be "prodromal LBD" in keeping with McKeith et al. (2016) but then biomarker assessment and strict clinical observation may help predicting diverging trajectories. In the near future, cerebrospinal fluid or molecular neuroimaging alpha-

synuclein selective biomarkers could be able to further clarify the neuropathological profile in vivo.

Disclosure statement

Dario Arnaldi has received fees from Fidia Farmaceutici (Italy) for lectures. Matteo Pardini reports research support from Novartis, speaker honoraria from Merk and Novartis and travel expenses for attending meetings from Merk, Novartis, Roche and Teva. The other authors have nothing to disclose.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.12.001.

References

Akhtar, R.S., Xie, S.X., Chen, Y.J., Rick, J., Gross, R.G., Nasrallah, I.M., Van Deerlin, V.M., Trojanowski, J.Q., Chen-Plotkin, A.S., Hurtig, H.I., Siderowf, A.D., Dubroff, J.G., Weintraub, D., 2017. Regional brain amyloid-β accumulation associates with domain-specific cognitive performance in Parkinson disease without dementia. PLoS One 12, e0177924.

Arnaldi, D., De Carli, F., Famà, F., Brugnolo, A., Girtler, N., Picco, A., Pardini, M., Accardo, J., Proietti, L., Massa, F., Bauckneht, M., Morbelli, S., Sambuceti, G., Nobili, F., 2017. Prediction of cognitive worsening in de novo Parkinson's disease: clinical use of biomarkers. Mov. Disord. 32, 1738–1747.

Berg, D., Postuma, R.B., Bloem, B., Chan, P., Dubois, B., Gasser, T., Goetz, C.G., Halliday, G.M., Hardy, J., Lang, A.E., Litvan, I., Marek, K., Obeso, J., Oertel, W., Olanow, C.W., Poewe, W., Stern, M., Deuschl, G., 2014. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov. Disord. 29, 454–462.

Boeve, B.F., Molano, J.R., Ferman, T.J., Smith, G.E., Lin, S.C., Bieniek, K., Haidar, W., Tippmann-Peikert, M., Knopman, D.S., Graff-Radford, N.R., Lucas, J.A., Petersen, R.C., Silber, M.H., 2011. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep Med. 12, 445–453.

Boeve, B.F., Dickson, D.W., Duda, J.E., Ferman, T.J., Galasko, D.R., Galvin, J.E., Goldman, J.G., Growdon, J.H., Hurtig, H.I., Kaufer, D.I., Kantarci, K., Leverenz, J.B., Lippa, C.F., Lopez, O.L., McKeith, I.G., Singleton, A.B., Taylor, A., Tsuang, D., Weintraub, D., Zabetian, C.P., 2016. Arguing against the proposed definition changes of PD. Mov. Disord. 31, 1619–1622.

Bohnen, N.I., Koeppe, R.A., Minoshima, S., Giordani, B., Albin, R.L., Frey, K.A., Kuhl, D.E., 2011. Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. J. Nucl. Med. 52, 848–855.

Briner, H.R., Simmen, D., 1999. Smell diskettes as screening test of olfaction. Rhinology 37, 145–148.

Burn, D.J., Rowan, E.N., Allan, L.M., Molloy, S., O'Brien, J.T., McKeith, I.G., 2006. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J. Neurol. Neurosurg. Psychiatry 77, 585–589.

Calvini, P., Rodriguez, G., Inguglia, F., Mignone, A., Guerra, U.P., Nobili, F., 2007. The basal ganglia matching tools package for striatal uptake semi-quantification: description and validation. Eur. J. Nucl. Med. Mol. Imaging 34, 1240–1253.

Capitani, E., Laiacona, M., 2000. Classification and modelling in neuropsychology: from groups to single cases. In: Boller, F., Grafman, J. (Eds.), Handbook of Neuropsychology, I. Elsevier, Amsterdam, NL, pp. 53–76.

Chen, B., Wang, S., Sun, W., Shang, X., Liu, H., Liu, G., Gao, J., Fan, G., 2017. Functional and structural changes in gray matter of Parkinson's disease patients with mild cognitive impairment. Eur. J. Radiol. 93, 16–23.

Darcourt, J., Booij, J., Tatsch, K., Varrone, A., Vander Borght, T., Kapucu, O.L., Någren, K., Nobili, F., Walker, Z., Van Laere, K., 2010. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur. J. Nucl. Med. Mol. Imaging 37, 443–450.

Darweesh, S.K.L., Wolters, F.J., Postuma, R.B., Stricker, B.H., Hofman, A., Koudstaal, P.J., Ikram, M.K., Ikram, M.A., 2017a. Association between poor cognitive functioning and risk of incident parkinsonism: the Rotterdam study. JAMA Neurol. 74, 1431–1438.

Darweesh, S., Verlinden, V., Stricker, B., Hofman, A., Koudstaal, P., Ikram, M.A., 2017b. Trajectories of prediagnostic functioning in Parkinson's disease. Brain 140, 429–441.

Donaghy, P.C., McKeith, I.G., 2014. The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis. Alzheimers Res. Ther. 6, 46.

Fengler, S., Liepelt-Scarfone, I., Brockmann, K., Schäffer, E., Berg, D., Kalbe, E., 2017. Cognitive changes in prodromal Parkinson's disease: a review. Mov. Disord. 32, 1655–1666.

Firbank, M.J., Yarnall, A.J., Lawson, R.A., Duncan, G.W., Khoo, T.K., Petrides, G.S., O'Brien, J.T., Barker, R.A., Maxwell, R.J., Brooks, D.J., Burn, D.J., 2017. Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. J. Neurol. Neurosurg. Psychiatry 88, 310–316.

Foltynie, T., Brayne, C.E., Robbins, T.W., Barker, R.A., 2004. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 127, 550–560.

Fujishiro, H., Nakamura, S., Sato, K., Iseki, E., 2015. Prodromal dementia with Lewy bodies. Geriatr. Gerontol. Int. 15, 817–826.

Garcia-Garcia, D., Clavero, P., Gasca Salas, C., Lamet, I., Arbizu, J., Gonzalez-Redondo, R., Obeso, J.A., Rodriguez-Oroz, M.C., 2012. Posterior parieto-occipital hypometabolism may differentiate mild cognitive impairment from dementia in Parkinson's disease. Eur. J. Nucl. Med. Mol. Imaging 39, 1767–1777.

Gelb, D.J., Oliver, E., Gilman, S., 1999. Diagnostic criteria for Parkinson disease. Arch. Neurol. 56, 33–39.

Gomperts, S.N., Locascio, J.J., Makaretz, S.J., Schultz, A., Caso, C., Vasdev, N., Sperling, R., Growdon, J.H., Dickerson, B.C., Johnson, K., 2016. Tau Positron emission tomographic imaging in the Lewy body diseases. JAMA Neurol. 73, 1334–1341.

González-Redondo, R., García-García, D., Clavero, P., Gasca-Salas, C., García-Eulate, R., Zubieta, J.L., Arbizu, J., Obeso, J.A., Rodríguez-Oroz, M.C., 2014. Grey matter hypometabolism and atrophy in Parkinson's disease with cognitive impairment: a two-step process. Brain 137, 2356–2367.

Halliday, G., Lees, A., Stern, M., 2011. Milestones in Parkinson's disease-clinical and pathological features. Mov. Disord. 26, 1015–1021.

Holtbernd, F., Gagnon, J.F., Postuma, R.B., Ma, Y., Tang, C.C., Feigin, A., Dhawan, V., Vendette, M., Soucy, J.P., Eidelberg, D., Montplaisir, J., 2014. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology 82, 620–627.

Huang, C., Mattis, P., Perrine, K., Brown, N., Dhawan, V., Eidelberg, D., 2008. Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease. Neurology 70, 1470–1477.

Huang, S.H., Chang, C.C., Lui, C.C., Chen, N.C., Lee, C.C., Wang, P.W., Jiang, C.F., 2015. Cortical metabolic and nigrostriatal abnormalities associated with clinical stage-specific dementia with Lewy bodies. Clin. Nucl. Med. 40, 26–31.

Ibarretxe-Bilbao, N., Junque, C., Marti, M.J., Tolosa, E., 2011. Brain structural MRI correlates of cognitive dysfunctions in Parkinson's disease. J. Neurol. Sci. 310, 70–74.

Marchand, D., Postuma, R.B., Escudier, F., De Roy, J., Pelletier, A., Montplasir, J., Gagnon, J.F., 2018. How does dementia with Lewy bodies start? Prodromal cognitive changes in REM sleep behavior disorder. Ann. Neurol. 83, 1016–1026.

McKeith, I., Taylor, J.P., Thomas, A., Donaghy, P., Kane, J., 2016. Revisiting DLB diagnosis: a consideration of prodromal DLB and of the diagnostic overlap with Alzheimer disease. J. Geriatr. Psychiatry Neurol. 29, 249–253.

McKeith, I.G., Boeve, B.F., Dickson, D.W., Halliday, G., Taylor, J.P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C.G., Bayston, A., Beach, T.G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J.E., El-Agnaf, O., Feldman, H., Ferman, T.J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J.G., Gomperts, S.N., Graff-Radford, N.R., Honig, L.S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V.M.Y., Leverenz, J.B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T.J., Moreno, E., Mori, E., Murray, M., O'Brien, J.T., Orimo, S., Postuma, R.B., Ramaswamy, S., Ross, O.A., Salmon, D.P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J.B., Trojanowski, J.Q., Tsuang, D., Walker, Z., Yamada, M., Kosaka, K., 2017. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89, 88–100.

Meles, S.K., Renken, R.J., Janzen, A., Vadasz, D., Pagani, M., Arnaldi, D., Morbelli, S., Nobili, F., Mayer, G., Leenders, K.L., Oertel, W.H.O., 2018. The metabolic pattern of idiopathic REM sleep behavior disorder reflects early-stage Parkinson's disease. J. Nucl. Med. 117, 202242.

Meyer, P.T., Frings, L., Hellwig, S., 2014. Update on SPECT and PET in parkinsonism - part 2: biomarker imaging of cognitive impairment in Lewy-body diseases. Curr. Opin. Neurol. 27, 398–404.

Morbelli, S., Drzezga, A., Perneczky, R., Frisoni, G.B., Caroli, A., van Berckel, B.N., Ossenkoppele, R., Guedj, E., Didic, M., Brugnolo, A., Sambuceti, G., Pagani, M., Salmon, E., Nobili, F., 2012. Resting metabolic connectivity in prodromal Alzheimer's disease. A European Alzheimer Disease Consortium (EADC) project. Neurobiol. Aging 33, 2533–2550.

Muslimovic, D., Post, B., Speelman, J.D., Schmand, B., 2005. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 65, 1239–1245.

Nobili, F., Campus, C., Arnaldi, D., De Carli, F., Cabassi, G., Brugnolo, A., Dessi, B., Morbelli, S., Sambuceti, G., Abbruzzese, G., Rodriguez, G., 2010. Cognitive-nigrostriatal relationships in de novo, drug-naïve Parkinson's disease patients: a [I-123]FP-CIT SPECT study. Mov. Disord. 25, 35–43.

Ossenkoppele, R., Jansen, W.J., Rabinovici, G.D., Knol, D.L., van der Flier, W.M., van Berckel, B.N., Scheltens, P., Visser, P.J., , Amyloid PET Study Group, Verfaillie, S.C., Zwan, M.D., Adriaanse, S.M., Lammertsma, A.A., Barkhof, F., Jagust, W.J., Miller, B.L., Rosen, H.J., Landau, S.M., Villemagne, V.L., Rowe, C.C., Lee, D.Y., Na, D.L., Seo, S.W., Sarazin, M., Roe, C.M., Sabri, O., Barthel, H., Koglin, N., Hodges, J., Leyton, C.E., Vandenberghe, R., van Laere, K., Drzezga, A., Forster, S., Grimmer, T., Sánchez-Juan, P., Carril, J.M., Mok, V., Camus, V., Klunk, W.E., Cohen, A.D., Meyer, P.T., Hellwig, S., Newberg, A., Frederiksen, K.S., Fleisher, A.S., Mintun, M.A., Wolk, D.A., Nordberg, A., Rinne, J.O., Chételat, G., Lleo, A., Blesa, R.,

Fortea, J., Madsen, K., Rodrigue, K.M., Brooks, D.J., 2015. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA 313, 1939–1949.
Pagani, M., Nobili, F., Morbelli, S., Arnaldi, D., Giuliani, A., Öberg, J., Girtler, N., Brugnolo, A., Picco, A., Bauckneht, M., Piva, R., Chincarini, A., Sambuceti, G., Jonsson, C., De Carli, F., 2017. Early identification of MCI converting to AD: a FDG PET study. Eur. J. Nucl. Med. Mol. Imaging 44, 2042–2052.
Pappatà, S., Santangelo, G., Aarsland, D., Vicidomini, C., Longo, K., Bronnick, K., Amboni, M., Erro, R., Vitale, C., Caprio, M.G., Pellecchia, M.T., Brunetti, A., De Michele, G., Salvatore, M., Barone, P., 2011. Mild cognitive impairment in drug-naive patients with PD is associated with cerebral hypometabolism. Neurology 77, 1357–1362.
Pausch, C., Schomburg, R., Wagenpfeil, S., Wollenweber, F.A., Bayer, C., Fassbender, K., Behnke, S., 2016. Neuropsychological impairment in prodromal Parkinson's disease. J. Neurol. Sci. 371, 117–120.
Petrou, M., Dwamena, B.A., Foerster, B.R., MacEachern, M.P., Bohnen, N.I., Müller, M.L., Albin, R.L., Frey, K.A., 2015. Amyloid deposition in Parkinson's disease and cognitive impairment: a systematic review. Mov. Disord. 30, 928–935.
Pilotto, A., Premi, E., Caminiti, S., Presotto, L., Turrone, R., Alberici, A., Paghera, B., Borroni, B., Padovani, A., Perani, D., 2018. Single-subject SPM FDG-PET patterns predict risk of dementia progression in Parkinson disease. Neurology 90, e1029–e1037.
Postuma, R.B., Berg, D., Stern, M., Poewe, W., Olanow, C.W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A.E., Halliday, G., Goetz, C.G., Gasser, T., Dubois, B., Chan, P., Bloem, B.R., Adler, C.H., Deuschl, G., 2015. MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. 30, 1591–1601.
Postuma, R.B., Berg, D., Stern, M., Poewe, W., Olanow, C.W., Oertel, W., Marek, K., Litvan, I., Lang, A.E., Halliday, G., Goetz, C.G., Gasser, T., Dubois, B., Chan, P., Bloem, B.R., Adler, C.H., Deuschl, G., 2016. Abolishing the 1-year rule: how much evidence will Be enough? Mov. Disord. 31, 1623–1627.
Ransmayr, G., Seppi, K., Donnemiller, E., Luginger, E., Marksteiner, J., Riccabona, G., Poewe, W., Wenning, G.K., 2001. Striatal dopamine transporter function in dementia with Lewy bodies and Parkinson's disease. Eur. J. Nucl. Med. 28, 1523–1528.
Ruffmann, C., Calboli, F.C., Bravi, I., Gveric, D., Curry, L.K., de Smith, A., Pavlou, S., Buxton, J.L., Blakemore, A.I., Takousis, P., Molloy, S., Piccini, P., Dexter, D.T., Gentleamn, S.M., Middleton, L.T., 2016. Cortical Lewy bodies and Ab burden are associated with prevalence and timingof dementia in Lewy body diseases. Neuropathol. Appl. Neurobiol. 42, 436–450.
Sauerbier, A., Jenner, P., Todorova, A., Chaudhuri, K.R., 2016. Non motor subtypes and Parkinson's disease. Parkinsonism Relat. Disord. 22 (Suppl 1), S41–S46.
Savica, R., Grossardt, B.R., Bower, J.H., Boeve, B.F., Ahlskog, J.E., Rocca, W.A., 2013. Incidence of dementia with Lewy bodies and Parkinson disease dementia. JAMA Neurol. 70, 1396–1402.
Scaglione, C., Vignatelli, L., Plazzi, G., Marchese, R., Negrotti, A., Rizzo, G., Lopane, G., Bassein, L., Maestri, M., Bernardini, S., Martinelli, P., Abbruzzese, G., Calzetti, S., Bonuccelli, U., Provini, F., Coccagna, G., Bologna, Genova, Parma and Pisa Universities group for the study of REM Sleep Behavior Disorder in Parkinson's Disease, 2005. REM sleep behaviour disorder in Parkinson's disease: a questionnaire-based study. Neurol. Sci. 25, 316–321.
Schrag, A., Horsfall, L., Walters, K., Noyce, A., Petersen, I., 2014. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 14, 57–64.
Shoji, Y., Nishio, Y., Baba, T., Uchiyama, M., Yokoi, K., Ishioka, T., Hosokai, Y., Hirayama, K., Fukuda, H., Aoki, M., Hasegawa, T., Takeda, A., Mori, E., 2014. Neural substrates of cognitive subtypes in Parkinson's disease: a 3-year longitudinal study. PLoS One 9, e110547.
Shokouhi, S., Claassen, D., Kang, H., Ding, Z., Rogers, B., Mishra, A., Riddle, W.R., Alzheimer's Disease Neuroimaging Initiative, 2013. Longitudinal progression of cognitive decline correlates with changes in the spatial pattern of brain 18F-FDG PET. J. Nucl. Med. 54, 1564–1569.
Spinnler, H., Tognoni, G., 1987. Standardizzazione e Taratura Italiana di Test Neuropsicologici. Ital. J. Neurol. Sci. 6 (Suppl 8), 1–127.
Tang, C.C., Poston, K.L., Dhawan, V., Eidelberg, D., 2010. Abnormalities in metabolic network activity precede the onset of motor symptoms in Parkinson's disease. J. Neurosci. 30, 1049–1056.
Tard, C., Demailly, F., Delval, A., Semah, F., Defebvre, L., Dujardin, K., Moreau, C., 2015. Hypometabolism in posterior and temporal areas of the brain is associated with cognitive decline in Parkinson's disease. J. Parkinsons Dis. 5, 569–574.
Vallar, G., Papagno, C., 2007. La diagnosi neuropsicologica. Normalità e patologia dal punto di vista statistico. Manuale di neuropsicologia. Il Mulino, Bologna, I, pp. 63–82.
Varrone, A., Asenbaum, S., Vander Borght, T., Booij, J., Nobili, F., Någren, K., Darcourt, J., Kapucu, O.L., Tatsch, K., Bartenstein, P., Van Laere, K., European Association of Nuclear Medicine Neuroimaging Committee, 2009. EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. Eur. J. Nucl. Med. Mol. Imaging 36, 2103–2110.
Weintraub, D., Chahine, L.M., Hawkins, K.A., Siderowf, A., Eberly, S., Oakes, D., Seibyl, J., Stern, M.B., Marek, K., Jennings, D., PARS Investigators, 2017. Cognition and the course of prodromal Parkinson's disease. Mov. Disord. 32, 1640–1645.
Weintraub, D., Tröster, A.I., Marras, C., Stebbins, G., 2018. Initial cognitive changes in Parkinson's disease. Mov. Disord. 33, 511–519.