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ORIGINAL COMMUNICATION

Beyond 35 years of Parkinson's disease: a comprehensive clinical and instrumental assessment

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Abstract

Background We sought to characterize the clinical, neuropsychological, electrophysiological, and neuroimaging features of Parkinson's disease (PD) after over 35 years since the onset of motor symptoms.

Methods Five consecutively consenting PD patients treated with subthalamic nucleus deep brain stimulation (STN-DBS) were recruited in a cross-sectional study of motor (Unified PD Rating Scale section-III), non-motor (Non-Motor Symptoms Scale), autonomic (Scale for Outcome in PD-Autonomic), and neuropsychological features associated with the very advanced phase of PD. In addition, patients underwent neurophysiological (autonomic tests and nerve conduction studies) and neuroimaging (brain MRI, ^{123}I-FP-CIT SPECT, and ^{123}I-MIBG myocardial scintigraphy) studies, as well as a genetic analysis of 34 genes and single nucleotide polymorphisms associated with PD.

Results There was a sustained motor response to L-dopa (range 14.4–35.6%), STN-DBS (23.3–38.4%), and L-dopa plus STN-DBS (37.8–63.0%). There were mild-to-moderate non-motor symptoms (range 19–83 on a scale of 0 to 360) and autonomic dysfunction (8–28 on a scale of 0–69). Two patients were demented, one had mild cognitive impairment, and two were cognitively preserved. Three patients had a sensory-axonal peripheral neuropathy and two a moderate-to-severe autonomic neuropathy. All cases showed a complete nigro-striatal dopaminergic denervation and a severe cardiovascular noradrenergic denervation. The brain MRI revealed only moderate frontal atrophy. The genetic tests were unremarkable.

Conclusions Even after more than 35 years of disease, L-dopa and STN-DBS remain effective on PD cardinal symptoms. Although axial, autonomic, and neuropsychological features may become key determinants of disability, some patients maintain a satisfactory quality of life, without significant motor and non-motor impairment.

Keywords Parkinson's disease · Deep brain stimulation · Late stage

Introduction

Despite a unifying hallmark, consisting of Lewy body deposition in the central nervous system, pathological aspects at the basis of Parkinson's disease (PD) motor and non-motor symptoms remain incompletely understood, partly due to a neurodegenerative process that involves multiple pathways including, but not limited to, dopaminergic, noradrenergic, serotoninergic, and cholinergic systems [1].

Advanced neurosurgical and infusion therapies, such as Deep Brain Stimulation (DBS), Levodopa/Carbidopa intestinal gel infusion, and Subcutaneous Apomorphine Infusion have significantly improved the long-term management of PD-related motor complications and the survival rate of patients with advanced PD [2–4]. As a result, an increasing portion of patients is reaching a stage in which the disability conveyed by PD motor symptoms is compounded by the functional impairment associated with axial and non-motor complications [5].

Nevertheless, only few studies have reviewed and analyzed features associated with very long-term PD progression [6–8] and, critically, no one of these studies has provided a detailed characterization of motor and non-motor symptoms. The extent to which motor and non-motor complications are represented at different stages of disease

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progression remains, in fact, to be clarified, as well as the disability conveyed by axial and non-motor symptoms in the very advanced phase of PD.

We sought to address these important points with a comprehensive clinical, neuropsychological, electrophysiological, and neuroimaging characterization of the population of PD patients with over 35 years of PD treated with subthalamic nucleus (STN)-DBS at our Movement Disorder Center.

Methods

Study population

We recruited in a cross-sectional study all patients with idiopathic PD, as per the UK Brain Bank criteria [9], with at least 35 years of PD duration treated with bilateral STN-DBS at our Centre. All patients underwent a clinical and neuropsychological pre-surgical evaluation, as per the "Core assessment program for surgical interventional therapies in Parkinson's disease—CAPSIT-PD" [10]. The ethical committee approval was obtained (*Comitato Etico Interaziendale Città della Salute e della Scienza di Torino*; CS/855; protocol number 475); a written informed consent was obtained from the patients. The demented patients gave their informed assent, and a written informed consent was obtained from their legal representative, in both cases the spouse.

Assessment

An extensive clinical, neuropsychological, instrumental, and genetic assessment was performed as per the following protocol.

Clinical evaluation

Patients were evaluated with a complete Unified Parkinson's Disease Rating Scale (UPDRS) [11]. The motor section (UPDRS part III) was performed in the four possible clinical conditions: Medication-OFF/Stimulation-OFF, Medication-ON/Stimulation-OFF, Medication-OFF/Stimulation-ON, and Medication-ON/Stimulation-ON. The UPDRS axial sub-score was calculated by the sum of items 18 (speech), 22 (neck rigidity), 27 (arising from a chair), 28 (posture), 29 (gait), 30 (postural stability) [12]. Additional clinical scales included the Non-Motor Symptoms Scale (NMSS) [13], the Schwab and England activities of daily living scale [14], and the PD Questionnaire 39 (PDQ-39) [15]. Dysphagia was evaluated and rated as per the Dysphagia Severity Scale [16], by a specialist after a fibroscopic evaluation.

Medications were logged and the L-dopa equivalent daily dose (LEDD) was calculated [17].

Neuropsychological assessment

Patients underwent a standardized cognitive test battery assessing reasoning, memory and frontal executive functions [18], the Beck Depression Inventory (BDI) [19], the State-Trait Anxiety Inventory [20] and the Marin Apathy Scale were applied [21]. PD mild cognitive impairment (PD-MCI) and PD dementia (PD-D) were defined according to the Movement Disorders Society criteria [22, 23].

Autonomic and peripheral symptoms assessment

The Scale for Outcome in Parkinson's Disease-Autonomic (SCOPA-AUT) [24], four limbs nerve conduction studies, and a standardized battery of autonomic tests, including the measurements of heart rate variability and beat-to-beat blood pressure monitoring during the Valsalva maneuver, deep breathing, and lying-to-standing test and blood pressure (BP) response to handgrip, as well as a 24-h ambulatory BP monitoring were used to evaluate autonomic functions. Orthostatic hypotension was defined as a fall in systolic BP of at least 20 mmHg or diastolic BP of at least 10 mmHg within 3 min of standing [25]. The response to handgrip was considered abnormal when diastolic BP increased more than 16 mmHg [26]. Cardiovascular autonomic neuropathy was defined by at least two abnormal parasympathetic tests and at least one abnormal sympathetic test [27].

Neuroimaging assessment

The neuroimaging assessment consisted of:

- Brain MRI (1.5 T; T1, T2, FLAIR, Gradient Echo sequences);
- Single Photon Emission Tomography (^{123}I-FP-CIT SPECT) was rated as per the following semi-quantitative scale [28]: "Abnormal—grade 1" (asymmetric uptake with normal putaminal activity in one hemisphere and a reduction in the contralateral putamen); "Abnormal—grade 2" (significant bilateral reduction in putamen uptake with normal/almost normal activity in the caudate); "Abnormal—grade 3" (virtually absent uptake bilaterally in both putamen and caudate).
- ^{123}I-MIBG myocardial scintigraphy tracer uptake was measured within both heart and mediastinum ROIs to calculate the heart to mediastinum (H/M) uptake ratio. Postsynaptic myocardial denervation was defined as a H/M ratio < 1.6 [29].

Genetic testing

A custom panel of 34 genes, including monogenic PD mutation and variants associated with increased risk of PD, was

designed with the HaloPlex online design tool (SureDesign, Agilent Technologies) and sequenced on MiSeq platform (Illumina, Inc., San Diego, CA, USA) using a Next Generation Sequencing approach.

Results

The prevalence of patients with PD duration ≥ 35 years followed up at our Center was 2% (5/255). All patients (4 males and 1 female) agreed to participate in the study. Demographic and clinical characteristics are summarized in Table 1.

Patient 1 was a 76-year-old male. His first PD symptom consisted of upper limb tremor starting at the age of 40. After 10 years of optimal response to oral dopaminergic therapies, he developed severe motor fluctuations in the form of peak-dose dyskinesia and wearing off. Concomitant medical conditions consisted of simple partial seizures, treated with lamotrigine, and benign prostatic hypertrophy (BPH). At the age of 63, he underwent STN-DBS with significant improvement of motor complications. At the time of surgery, he had moderately disabling L-dopa-induced dyskinesia, mild resting tremor, moderate-to-severe bradykinesia and rigidity, and moderate gait and postural instability in the OFF-condition. After 13 years of treatment with STN-DBS, dyskinesia affected him for less than 25% of his waking day and he spent less than 25% of his waking day in OFF. He reported constipation, hyposmia, drooling, and REM sleep behavior disorder (RBD). His motor, non-motor, cognitive,

Table 1 Demographic and clinical features

Demographic features	
Age (years)	72.4 ± 4.9 (67–76)
Age at PD onset (years)	35.6 ± 5.8 (27–40)
Disease duration (years)	36.8 ± 1.9 (35–40)
STN-DBS duration (years)	14.6 ± 1.5 (13–16)
Therapy features	
Total LEDD (mg)	661.5 ± 389.7 (200–1175)
Motor symptoms features	
UPDRS-III Med-OFF/Stim-OFF	73.2 ± 9.9 (64–90)
Axial sub-score	19.8 ± 2.7 (18–24)
UPDRS-III Med-OFF/Stim-ON	47.5 ± 12.8 (35–68)
Axial sub-score	14.9 ± 3.6 (12–21)
UPDRS-III Med-ON/Stim-OFF	59.0 ± 16.2 (37–82)
Axial sub-score	17.6 ± 4.7 (11–23)
UPDRS-III Med-ON/Stim-ON	34.6 ± 10.8 (29–54)
Axial sub-score	12.4 ± 3.5 (9–18)
UPDRS-IV	8.2 ± 2.6 (5–11)
Dyskinesia duration (item 32)	1.4 ± 1.1 (0–3)
Dyskinesia severity (item 33)	0.8 ± 0.8 (0–2)
Percentage of waking day spent in OFF (item 39)	1.2 ± 0.4 (1–2)
Non-motor symptoms features	
NMSS	56.8 ± 27.5 (19–83)
SCOPA-AUT	19.0 ± 9.7 (8–28)
Activities of daily living and quality of life features	
UPDRS-II Med-OFF	25.8 ± 2.6 (23–30)
UPDRS-II Med-ON	17.2 ± 5.4 (10–22)
S&E Scale Med-OFF	45 ± 16.6 (25–60)
S&E Scale Med-ON	65 ± 22.4 (35–90)
PDQ-39 S-I	46.2 ± 16.7 (24.7–60.1)

Results are reported as average ± standard deviation (min–max)

LEDD levodopa equivalent daily dose, *NMSS* Non-Motor Symptoms Scale (range 0–360), *PDQ-39 S-I* Parkinson's Disease Questionnaire Single Index (range 0–100), *SCOPA-AUT* Scale for Outcome in Parkinson's Disease-Autonomic (range 0–69), *S&E Scale* Schwab and England Scale (range 0–100), *STN-DBS* Subthalamic Nucleus Deep Brain Stimulation, *UPDRS* Unified Parkinson's Disease Rating Scale (section-II range 0–52; section-III range 0–108; section-III axial range 0–24; section-IV range 0–20; item 32, 33 and 39 range 0–4)

radiological, autonomic, and genetic assessment is summarized in Tables 2, 3 and 4.

Patient 2 was a 67-year-old female who developed PD at the age of 27. Initial symptoms consisted of resting tremor and bradykinesia involving the right upper limb. After 18 years of management with oral medications, she developed disabling peak-dose dyskinesia and wearing-off refractory to oral treatments. She underwent STN-DBS surgery at the age of 51. At the time of surgery, she had moderately disabling L-dopa-induced dyskinesia, mild resting tremor, severe bradykinesia and rigidity, moderate gait impairment and severe postural instability in the OFF-condition. After 16 years of STN-DBS treatment, the percentage of waking day spent in OFF was 10%. The percentage of the day spent with mild dyskinesia was 15%. She used a wheelchair for long-distance transportations. She reported constipation, hyposmia, drooling, mild urge-incontinence, moderate dysphagia, and severe speech impairment. Her motor, non-motor, cognitive, radiological, autonomic, and genetic assessment is summarized in Tables 2, 3 and 4.

Patient 3 was a 76-year-old male. His first symptoms were rigidity and bradykinesia at the right upper limb, starting at the age of 39. After 16 years of management with oral dopaminergic therapies he developed disabling motor fluctuations, in particular wearing-off. Concomitant medical conditions consisted of BPH. At the age of 60 he underwent STN-DBS. At the time of surgery, he had severely disabling L-dopa-induced dyskinesia, mild-to-moderate bradykinesia and rigidity, moderate gait impairment and mild postural instability in the OFF-condition. After 16 years of STN-DBS, the percentage of waking day spent in OFF was 25%. The percentage of waking day spent with dyskinesia was 55%. He reported mild constipation, hyposmia, drooling, RBD, moderate swallowing problems. Significant state/trait anxiety and apathy were also present. His motor, non-motor, cognitive, radiological, autonomic, and genetic assessment is summarized in Tables 2, 3 and 4.

Patient 4 was a 76-year-old male with PD onset at the age of 40. His first symptoms consisted of rigidity and bradykinesia involving the left upper limb. After 15 years of good response to dopaminergic therapies, he developed motor fluctuation, with peak-dose dyskinesia and wearing-off. At the age of 61 he underwent STN-DBS surgery. At the time of surgery, he had moderately disabling L-dopa-induced dyskinesia, mild resting tremor, mild-to-moderate bradykinesia and rigidity, moderate gait impairment and mild postural instability in the OFF-condition. After 15 years of STN-DBS treatment, dyskinesia affected him for 30% of his waking day and he reported to spend 30% of his waking day in OFF. He reported mild constipation, hyposmia, drooling, RBD, mild dysphagia, mild mood depression, and anxiety. His motor, non-motor, cognitive, radiological, autonomic, and genetic assessment is summarized in Tables 2, 3 and 4.

Table 2 UPDRS subscales—response to levodopa and STN-DBS

	UPDRS-I	UPDRS-II (OFF)	UPDRS-II (ON)	UPDRS-III/axial subscore (Med-OFF/Stim-OFF)	UPDRS-III/axial subscore (Med-ON/Stim-ON)	UPDRS-III/axial subscore (Med-ON/Stim-OFF)	UPDRS-III/axial subscore (Med-OFF/Stim-ON)	Response to L-dopa (%)	Response to STN-DBS (%)	Response to L-dopa + STN-DBS (%)	UPDRS-IV
1	6	26	10	73/18	27/10	47/11	45/12	35.6	38.4	63.0	11
2	7	23	22	90/24	56/18	77/23	69/21	14.4	23.3	37.8	5
3	4	30	20	70/21	35/13	58/21	47/13	17.1	32.9	50.0	10
4	7	25	21	69/18	35/12	56/16	49/15	18.8	29.0	49.3	6
5	3	25	13	64/18	25/9	48/17	40/13	25.0	37.5	60.9	9

The effect of L-dopa, STN-DBS and combined therapy (L-dopa plus STN-DBS) were considered as the improvement of the UPDRS-III comparing respectively the Med-OFF/Stim-OFF vs. Med-ON/Stim-OFF, Med-OFF/Stim-OFF vs. Med-OFF/Stim-ON and Med-OFF/Stim-OFF vs. Med-ON/Stim-ON

STN-DBS subthalamic nucleus deep brain stimulation, *UPDRS* Unified Parkinson's Disease Rating Scale (section-I range 0–16; section-II range 0–52; section-III range 0–108; section-III axial range 0–24; section-IV range 0–20)

Table 3 Clinical, instrumental, and imaging data

	Clinical phenotype	HY (Med-ON/Stim-ON)	Cognitive status	Falls	Freezing	Dysphagia	PN	Brain MRI	[(123)I] FP-CIT SPECT	(131) I-MIBG scintigraphy (*H/M* ratio)	CV autonomic neuropathy	BP-24 h monitoring	NMSS	SCOPA-AUT	S&E OFF/ON	PDQ-39 S-I
1	TD	2.5	sd-MCI	No	No	No	S-A	Nonspecific vascular lesions	Abnormal—Grade 3	Abnormal (1.11)	No	Normal	37	9	60//80	26.8
2	AR	4	Demented	Yes	Yes	Moderate	No	Mild fronto-temporal atrophy	Abnormal—Grade 3	Abnormal (1.09)	No	Normal	69	25	25//35	57.4
3	AR	3	Normal	Yes	Yes	Moderate	SM-A	Nonspecific vascular lesions	Abnormal—Grade 3	Abnormal (0.95)	Yes	No nocturnal dipping	76	25	50//70	57.2
4	AR	4	Demented	Yes	Yes	Mild	S-A	Mild fronto-temporal atrophy	Abnormal—Grade 3	Abnormal (1.05)	Yes	Reverse dipping	83	28	30//50	60.1
5	AR	2	Normal	No	No	Mild	No	Mild frontal atrophy	Abnormal—Grade 3	Abnormal (1.15)	No	No nocturnal dipping	19	8	60 // 90	31.4

AR akinetic-rigid, *BP* blood pressure, *CV* cardiovascular, *HY* Hoehn and Yahr Stage (range 0–5); *NMSS* Non-Motor Symptoms Scale (range 0–360), *PDQ-39 S-I* Parkinson's Disease Questionnaire Single Index (range 0–100), *PN* peripheral neuropathy (S-A Sensory-Axonal, *SM-A* Sensory–Motor-Axonal), *SCOPA-AUT* Scale for Outcome in Parkinson's Disease-Autonomic (range 0–69), *sd-MCI* single domain Mild Cognitive Impairment, *S&E* Schwab and England Scale (range 0–100), *TD* tremor dominant

Table 4 Non-motor, cognitive, autonomic, and genetic data

ID	#1	#2	#3	#4	#5
Non-motor symptoms assessment (NMSS domains)					
Cardiovascular/falls	4	0	21	8	0
Sleep/fatigue	6	8	16	13	5
Mod/cognition	3	6	10	11	3
Perceptual problems/hallucinations	0	3	1	4	0
Attention/memory	4	27	2	27	1
Gastro-intestinal tract	14	11	11	12	5
Urinary	2	3	6	1	1
Sexual function	0	4	2	3	0
Miscellaneous	4	7	7	4	4
Cognitive assessment[a]					
Reasoning					
CPM 47	1	3	0	3	1
Memory					
CBT	2	3	0	2	1
PAL	1	3	0	2	1
Attention					
DCT	1	3	1	3	1
TMA	1	3	1	3	0
Executive functions					
TMB	3	3	0	3	1
FAB	3	3	0	3	0
Language					
CVF	1	3	0	1	1
PVF	0	3	0	1	0
Autonomic and cardiovascular assessment					
Orthostatic hypotension	Asymptomatic ($\Delta = -25/12$)	No ($\Delta = -4/2$)	Symptomatic ($\Delta = -32/15$)	Symptomatic ($\Delta = -28/17$)	No ($\Delta = -13/8$)
HRV					
Deep breathing	Normal	Normal	Impaired	Normal	Normal
Valsalva maneuver	Normal	Normal	Impaired	Impaired	Normal
Lying to standing	Impaired	Normal	Impaired	Impaired	Normal
Genetic assessment					
Genetic panel[b]	Negative	Negative	Negative	Negative	Negative

CBT Corsi's block tapping test, *CPM 47* raven coloured progressive matrices, *CVF* category verbal fluency, *DCT* digit cancellation test, *FAB* frontal assessment battery, *HRV* heart rate variability, *NMSS* Non-Motor Symptoms Scale, *PAL* Paired Associate Learning, *PVF* Phonemic Verbal Fluency, *TMA* Trail Making Test A, *TMB* Trail Making Test B, *WST* Weigl Sorting Test

[a]0 = normal; 1 = limited performances; 2 = moderate impairment; 3 = severe impairment

[b]The NGS custom panel of 34 genes used for the sequencing analysis: *Genes associated to idiopathic PD and EOPD*: SNCA (PARK1), PRKN (PARK2), UCHL1 (PARK5), PINK1 (PARK6), DJ1 (PARK7), LRRK2 (PARK8), GBA, Omi/HTRA2, VPS35, EIF4G1, DNAJC6; *Genes associated to atypical forms of Parkinsonism*: ATP13A2, ATP6AP2, ATP7B, DNAJC13, FBXO7, GRN, HGSNAT, MAPT/STH, PANK2, PLA2G6, POLG1, SLC30A10, SPG11, SYNJ1, TARDBP, VPS13C; *Genes associated to genetic Dystonia conditions in differential diagnosis with PD*: GCH1 (DYT5), TH (DYT5), PRKRA (DYT16), SPR, TAF1 (DYT3), ATP1A3 (DYT12), SGCE (DYT11)

Patient 5 was a 67-year-old male with PD onset at the age of 32, presenting with bradykinesia at the right upper limb. After 17 years of management with oral dopaminergic therapies, he developed severely disabling peak-dose dyskinesia. At the age of 54 he underwent STN-DBS surgery. At the time of surgery, he had moderately disabling L-dopa-induced dyskinesia, mild resting tremor, moderate-to-severe bradykinesia and rigidity, severe gait impairment and moderate postural instability in the OFF-condition. After 13 years from STN-DBS he reported a good control of both dyskinesia and OFF periods, in both cases affecting him for less than 25% of the waking day. He reported

moderate speech impairment, mild constipation, hyposmia, RBD, and mild dysphagia. His motor, non-motor, cognitive, radiological, autonomic, and genetic assessment is summarized in Tables 2, 3 and 4.

Discussion

We reported an extensive clinical and instrumental characterization of 5 long-term surviving patients with over 35 years of PD, and observed that STN-DBS and L-dopa continued to remain effective on motor symptoms, even in the very advanced phase of PD. Only two patients (Patient 2 and 4) met the criteria for "late-stage" PD, namely severe axial or cognitive impairment, which suggest that severe functional disability is not a mandatory outcome in PD, even after 35 years of disease.

Still, the majority of patients was affected by disabling non-motor complications, consisting of constipation, hyposmia, RBD, and dysphagia. Two patients developed dementia, and one a single domain amnestic MCI. While cognitive decline is one of the features associated with the long-term progression of PD [5, 6, 30], we cannot exclude an effect due to the placement of the STN-DBS leads through the frontal lobes or to the stimulation of subthalamic associative areas [31]. Moreover, two patients had a severe autonomic neuropathy associated with symptomatic OH and one met the criteria for asymptomatic OH with only mild alterations at the autonomic testing. All of these patients had a sensory–motor axonal neuropathy, possibly due to the chronic exposure to L-dopa [32], to PD-associated peripheral neurodegeneration [33], or to a combination thereof. Non-motor and autonomic features were associated with higher axial symptoms severity (Patient 2, 3 and 4) and rate of falls, worse quality of life, and greater dependence in the ADL [34, 35]. Of interest, two patients (Patient 1 and 5) maintained a good quality of life, without significant motor and non-motor impairment.

Alterations at the functional imaging studies were consistently observed in all patients, with an almost complete depletion of the nuclear activity at the ^{123}I-FP-CIT SPECT and an important postsynaptic myocardial denervation at the ^{123}I-MIBG scintigraphy. Conventional MRI did not show any specific alterations, but only a mild sub-cortical, symmetrical frontal atrophy.

While an extensive panel of genetic analysis did not disclose any pathological mutations or genetic variant associated with PD, suggesting that not all cases of young-onset PD or mildly progressive PD are associated with genetic alterations, final conclusions cannot be drawn due to the limited number of cases. Other important limitations consist of the selection biases associated with the young onset, the long survival also due to the absence of detrimental comorbidities, and the relatively "benign" clinical phenotype of patients undergoing STN-DBS after an average PD duration of 22 years.

Taking into account these limitations, our main findings can be summarized as follows: (1) all patients reported a satisfactory response to L-dopa and STN-DBS despite the very long duration of PD motor symptoms and the almost complete nigro-striatal denervation. Of interest, the combined efficacy of STN-DBS and L-dopa was greater than each one of these therapies alone, suggesting a potential synergism; (2) axial and non-motor symptoms represented the main determinants of disability; (3) dementia and other non-motor complications do not represent a mandatory outcome in PD, even after more than 35 years since the onset of motor symptoms.

Author contributions AR: conception and design of the study; acquisition, analysis and interpretation of data; writing of the first draft and review and critique of the manuscript. MF: design of the study; acquisition, analysis and interpretation of data; writing of the first draft and review and critique of the manuscript. AM: design of the study; acquisition, analysis and interpretation of data; review and critique of the manuscript. EM: design of the study; acquisition, analysis and interpretation of data; review and critique of the manuscript. SP: design of the study; acquisition, analysis and interpretation of data; review and critique of the manuscript. TM: design of the study; analysis and interpretation of data; review and critique of the manuscript. AS: design of the study; analysis and interpretation of data; review and critique of the manuscript. SG: design of the study; analysis and interpretation of data; review and critique of the manuscript. MGR: conception and design of the study; analysis and interpretation of data; review and critique of the manuscript. LL: conception and design of the study; analysis and interpretation of data; review and critique of the manuscript. All the co-authors listed above gave their final approval of this manuscript version.

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Compliance with ethical standards

Conflicts of interest Dr. Romagnolo has received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco and UCB Pharma. Dr. Fabbri reports no disclosures. Dr. Merola is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL Behring, Abbvie, and Cynapsus Therapeutics. He has received grant support from Lundbeck. Dr. Montanaro reports no disclosures. Dr. Palermo reports no disclosures. Dr. Martone reports no disclosures. Dr. Seresini reports no disclosures. Dr. Goldwurm reports no disclosures. Dr. Rizzone has received honoraria for lecturing and travel grants from Medtronic and Zambon. Dr. Lopiano has received honoraria for lecturing and travel grants from Medtronic, UCB Pharma and AbbVie.

Ethical standard The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The local institutional review board (*Comitato Etico Interaziendale Città della Salute e della Scienza di Torino*; CS/855; protocol number 475) approved the study and all participants provided written informed consent. The demented patients gave their informed assent, and a written informed consent was obtained from their legal representative.

Data access and responsibility statement A. Romagnolo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Berg D, Postuma RB, Bloem B et al (2014) Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord 29:454–462
2. Bronstein JM, Tagliati M, Alterman RL et al (2011) Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol 68:165–171
3. Devos D, French DUODOPA, Study Group (2009) Patient profile, indications, efficacy and safety of duodenal levodopa infusion in advanced Parkinson's disease. Mov Disord 24:993–1000
4. García Ruiz PJ, Sesar Ignacio A, Ares Pensado B et al (2008) Efficacy of long-term continuous subcutaneous apomorphine infusion in advanced Parkinson's disease with motor fluctuations: a multicenter study. Mov Disord 23:1130–1136
5. Rizzone MG, Fasano A, Daniele A et al (2014) Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? Parkinsonism Relat Disord 20:376–381
6. Merola A, Zibetti M, Angrisano S et al (2011) Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients. Brain 134:2074–2084
7. Munhoz RP, Espay AJ, Morgante F et al (2013) Long-duration Parkinson's disease: role of lateralization of motor features. Parkinsonism Relat Disord 19:77–80
8. Pinter B, Diem-Zangerl A, Wenning GK et al (2015) Mortality in Parkinson's disease: a 38-year follow-up study. Mov Disord 30:266–269
9. Gibb WRG, Lees AJ (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 51:745–752
10. Defer GL, Widner H, Marié RM et al (1999) Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 14:572–584
11. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease (2003) The unified Parkinson's disease rating scale (UPDRS): status and recommendations. Mov Disord 18:738–750
12. Levy G, Louis ED, Cote L et al (2005) Contribution of aging to the severity of different motor signs in Parkinson disease. Arch Neurol 62:467–472
13. Chaudhuri KR, Martinez-Martin P, Brown RG et al (2007) The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord 22:1901–1911
14. Schwab RS, England AC (1969) Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML (eds) Third symposium on Parkinson's disease. E & S Livingston, Edinburgh, pp 152–157
15. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N (1997) The Parkinson's disease questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 26:353–357
16. O'Neil KH, Purdy M, Falk J, Gallo L (1999) The dysphagia outcome and severity scale. Dysphagia 14:139–145
17. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25:2649–2653
18. Merola A, Rizzi L, Artusi CA et al (2014) Subthalamic deep brain stimulation: clinical and neuropsychological outcomes in mild cognitive impaired parkinsonian patients. J Neurol 261:1745–1751
19. Beck AT (1987) Beck depression inventory. Psychological Corporation, San Antonio
20. Spielberger CD, Gorsuch RL, Lushene RE (1970) Manual for the state-trait anxiety inventory. Consulting Psychologist Press, Palo Alto
21. Marin RS (1991) Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 3:243–254
22. Litvan I, Goldman JG, Tröster AI et al (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 27:349–356
23. Emre M, Aarsland D, Brown R et al (2007) Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22:1689–1707
24. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ (2004) Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord 19:1306–1312
25. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M (2006) EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol 13:930–936
26. Boulton AJ, Vinik AI, Arezzo JC et al (2005) Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 28:956–962
27. Ewing DJ, Martyn CN, Young RJ, Clarke BF (1985) The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 8:491–498
28. Benamer TS, Patterson J, Grosset DG et al (2000) Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group. Mov Disord 15:503–510
29. Ishibashi K, Saito Y, Murayama S et al (2010) Validation of cardiac (123)I-MIBG scintigraphy in patients with Parkinson's disease who were diagnosed with dopamine PET. Eur J Nucl Med Mol Imaging 37:3–11
30. Fasano A, Romito LM, Daniele A et al (2010) Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. Brain 133:2664–2676
31. York MK, Dulay M, Macias A et al (2008) Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 79:789–795
32. Ceravolo R, Cossu G, Bandettini di Poggio M et al (2013) Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study. Mov Disord 28:1391–1397
33. Uncini A, Eleopra R, Onofrj M (2015) Polyneuropathy associated with duodenal infusion of levodopa in Parkinson's disease: features, pathogenesis and management. J Neurol Neurosurg Psychiatry 86:490–495
34. Lawson RA, Yarnall AJ, Duncan GW et al (2016) Cognitive decline and quality of life in incident Parkinson's disease: the role of attention. Parkinsonism Relat Disord 27:47–53
35. Merola A, Romagnolo A, Comi C et al (2017) Prevalence and burden of dysautonomia in advanced Parkinson's disease. Mov Disord 32:796–797

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