Movement Disorders
CLINICAL PRACTICE

Factors Associated with Health-Related Quality of Life in Late-Stage Parkinson's Disease

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ABSTRACT: Background: There is limited knowledge on health-related quality of life (HRQoL) in late-stage Parkinson's disease (PD).
Objective: To assess factors associated with HRQoL in patients with late-stage PD, with a focus on health care provision.
Methods: The Care of Late Stage Parkinsonism (CLaSP) project is the largest study on late-stage PD to date. The current study analyzed data of 401 patients from 6 European countries in whom HRQoL was assessed with the 8-item PD Questionnaire in patients without dementia. Factors potentially associated with HRQoL were assessed and examined in linear regression analyses.
Results: Better HRQoL was associated with living at home, greater independence in activities of daily living (Schwab and England Scale), less severe disease (Hoehn and Yahr stage), better motor function (Unified PD Rating Scale Part III), and lower non-motor symptoms burden (Non-Motor Symptoms Scale [NMSS]) across all NMSS domains. Having a PDspecialist as physician for PD, contact with a PDnurse, and no hospital admission during the past 3 months were associated with better HRQoL, but having seen a physiotherapist or occupational therapist was associated with worse HRQoL.
Conclusions: The results emphasize the importance of optimizing treatment for motor and multiple non-motor symptoms to improve HRQoL in patients with late-stage PD. PD-specific health care resources, particularly PDnurses, are likely important in addressing issues to improve HRQoL in this population. Worse HRQoL in those who had recently seen a physiotherapist or occupational therapist may reflect referral based on factors not measured in this study.

Parkinson's disease (PD) is a progressive disorder that currently can only be treated symptomatically.[1] In the late stage of the disease, that is, Hoehn and Yahr (HY) stages IV and V,[2] both motor and non–motor symptoms (NMS) are pronounced,[3–6] and a patient's life satisfaction is often reduced.[7] As the patients

become dependent on help in activities of daily living (ADL), there is an increasing burden on the patients' informal caregivers as well as an increasing demand on societal health and social care systems. Furthermore, these patients often lose contact with specialized PD health care, and their management often falls to

nonspecialist clinicians. Despite this, to date there is limited research or guidance on the pharmacological and non-pharmacological management of late-stage PD.[3]

Previous studies have shown that both motor and NMS affect health-related quality of life (HRQoL) in PD.[8] HRQoL is defined as the impact of health status on a person's quality of life (QoL), a multidimensional concept including physical, mental, emotional, and social functioning.[9] A person's perceived health status provides relevant information about individual functioning and well-being and constitutes an appropriate outcome measure in PD.[10] As improving HRQoL is the key aim in PD therapy, particularly in the late stage of the disease, identification of factors associated with patient HRQoL can help address these factors and focus future research to improve HRQoL in late-stage PD. The aim of this study was to describe and assess factors associated with HRQoL in late-stage PD with a special focus on health care provision.

Patients and Methods

Participants and Recruitment

Baseline data from the longitudinal multicenter cohort study Care of Late Stage Parkinsonism (CLaSP) were used. Details of this study can be found elsewhere.[11] Patients were recruited at 7 movement disorder centers in 6 European countries (the United Kingdom, Germany, the Netherlands, Portugal, France, and Sweden) with different health care systems. The goal of the project was to establish a large European cohort of patients in late-stage PD, defined as HY stages IV to V (score range 1–5, higher = worse)[2] while on medication and/or having a substantial need of help with ADL; ≤50% on the Schwab and England ADL Scale (score range 0–100, higher = better).[12] Patients were identified through various health care settings at the different centers: neurology departments; the municipality-based health care system; and care of the elderly, palliative care, and primary care settings.[11]

Inclusion criteria were HY stages IV and V[2] while on medication and/or having a substantial need of help with ADL (≤50% on the Schwab and England Scale)[12] as well as having been diagnosed with parkinsonism for a minimum of 7 years. Exclusion criteria were cognitive symptoms that started before the PD diagnosis as well as symptomatic parkinsonism (such as drug-induced parkinsonism or normal pressure hydrocephalus). For this study we only included patients without an established diagnosis of dementia.

Procedure and Clinical Evaluation

HRQoL was assessed by the 8-item PD Questionnaire (PDQ-8; score range 0–32, higher = worse), a PD-specific subjective measure of overall health status, which is a shorter form version derived from the PDQ-39. The results of the 2 instruments have been found to be highly similar, and the use of the shorter form has been recommended when a shorter version is needed or preferred.[13,14] The PDQ-8 includes 8 items, scored 0 to 4, from the 8 domains of the PDQ-39: mobility, ADL, emotional well-being, social support, cognition, communication, bodily discomfort, and stigma. The scores are summed, divided by the total possible, and given as a percentage score of 100.

Motor function was assessed by the motor part of the Unified PD Rating Scale Part III (UPDRS III, score range 0–108, higher = worse).[15] Non-motor symptomatology was assessed by the Non-Motor-Symptoms Scale (NMSS; score range 0–360, higher = worse).[16] The NMSS has 30 items that are grouped into 9 domains. Cognitive function was assessed with the Mini-Mental State Examination (MMSE, score range 0–30, higher = better).[17] Depressive symptoms were assessed by the Geriatric Depression Scale (GDS-15; score range 0–15, higher = worse).[18,19]

A study-specific resource utilization questionnaire for patients with PD and their informal caregivers was used to determine the use of health care as well as informal care resources.[11,20] A PDspecialist was here defined as a neurologist, geriatrician, or elderly care physician. A PDnurse is a nurse who has experience in working with patients with PD.

Information on patients' medication was collected and levodopa equivalent daily dose (LEDD) was calculated according to a standardized formula.[21]

Statistical Analyses

Descriptive and clinical data are given as median with first and third quartiles (q1–q3) and frequencies and percentages, as appropriate. Associations were tested statistically with simple linear regression analyses. For the multivariable PDQ-8 analyses, 20 independent variables with P values <0.3 from the simple linear regression analyses were simultaneously entered into a multivariable linear regression model to identify factors independently associated with HRQoL. A backward-stepping regression analysis was conducted where P values were inspected and the variable with the highest P value was manually removed from the model, which was repeated until the remaining independent variables in the model had P values <0.1. P values of <0.05 were considered significant. All analyses were performed using IBM SPSS version 26.0 (IBM Corporation, Armonk, NY).

Results

Demographic and Clinical Data

The study consisted of 401 patients. The number of patients from the different European countries were as follows: United Kingdom, n = 77 (19%); Germany, n = 121 (30%); France, n = 37 (9%); Sweden, n = 73 (18%); the Netherlands, n = 42 (10%); and Portugal, n = 51 (13%). The median (q1–q3) age was

TABLE 1 Demographic and clinical data of the patients with late-stage PD (n = 401)

Variables	Median (q1–q3) or n (%)	Missing, n
Age, yr	76 (70–81)	–
Sex, male	216 (54)	–
PD duration, yr	14 (10–19)	2
Age at onset, yr	60 (52–68)	2
HY stage	4 (4–4)	–
HY stage		
II–III	32 (8)	
IV	286 (71)	
V	83 (21)	
ADL independency, S&E	40 (30–50)	–
Dwelling place		–
Home	323 (81)	
Nursing home[a]	78 (19)	
Partner,[b] yes	262 (66)	1
LEDD, mg	825 (550–1195)	6
Clinical assessments		
Motor function, UPDRS III	41 (32–54)	2
Non-motor symptoms, NMSS	87 (56–122)	8
Non-motor symptoms, NMSS, domains		
Cardiovascular including falls	1 (0–4)	8
Sleep/fatigue	12 (6–20)	8
Mood/apathy	9 (4–23)	8
Perceptual problems/hallucinations	1 (0–6)	8
Attention/memory	6 (1–15)	8
Gastrointestinal tract	10 (4–16)	8
Urinary	12 (4–24)	8
Sexual function	3 (0–16)	8
Miscellaneous[c]	12 (5–18)	8
Cognition, MMSE	26 (24–28)	9
Depressive symptoms, GDS-15	6 (4–9)	89
Participants per country		–
United Kingdom	77 (19)	
Germany	121 (30)	
France	37 (9)	
Sweden	73 (18)	
The Netherlands	42 (10)	
Portugal	51 (13)	
Physician for PD[d]		38
GP	112 (31)	
PDspecialist[e]	295 (81)	
Neurologist	285 (79)	
Geriatrician	7 (2)	
Elderly care physician	3 (1)	
Other/do not know	12 (3)	
Contact for PD, past 3 mo		
GP	202 (56)	38
PDspecialist[e]	173 (48)	38
PDnurse	59 (16)	38
Physiotherapist	207 (57)	38
Occupational therapist	63 (17)	38
Speech and language therapist	78 (22)	38
Hospital admitted	96 (26)	38
Rehabilitation center inpatient, overnight	21 (6)	38
Rehabilitation center outpatient	11 (3)	38
Help from caregiver in daily life	304 (84)	40
Health-related quality of life assessment		
PDQ-8[f]	44 (34–56)	

PD, Parkinson's disease; q1-q3, first and third quartiles; HY, Hoehn and Yahr; ADL, activities of daily living; S&E, Schwab & England; LEDD, levodopa equivalent daily dose; UPDRS III, Unified PD Rating Scale, Part III, motor examination; NMSS, Non-Motor Symptoms Scale; MMSE, Mini-Mental State Examination; GDS-15, Geriatric Depression Scale; GP, general practitioner; PDQ-8, 8-item PD Questionnaire.

S&E ADL scale score range 0 to 100, higher = better.

HY staging scale score range I to V, higher = worse. UPDRS III score range 0 to 108, higher = worse. NMSS score range 0–360, higher = worse. MMSE score range 0 to 30, higher = better. GDS-15 score range 0 to 15, higher = worse. PDQ-8 (PD-specific health measure) score range 0 to 32, higher = worse.

[a]Nursing home, including long-term institutional care, intermediate forms of accommodation (eg, short-term care/respite care), and assisted living.

[b]Partner includes married, living apart, and partnership. No partner includes single, divorced, and widowed.

[c]Miscellaneous domain includes pain, change in ability to taste or smell, change in weight, and excessive sweating.

[d]There is slight overlap, as some patients see more than 1 category for their PD: neurologist + GP + geriatrician + elderly care physician.

[e]Neurologist/geriatrician/elderly care physician.

[f]In nondemented patients only.

TABLE 2 Simple linear regression analyses with PDQ-8 as the dependent variable (n = 401)

Independent Variables	Unstandardized Coefficient β (95% CI)	P Value	Controlled for Age and Sex	
			Unstandardized Coefficient β (95% CI)	P Value
Age, yr	−0.00 (−0.19 to 0.18)	0.970	-	-
Sex, male	0.85 (−2.46 to 4.15)	0.615	-	-
PD duration, yr	0.08 (−0.13 to 0.30)	0.459	0.08 (−0.14 to 0.29)	0.465
HY stage	2.73 (0.17 to 5.30)↓↓	**0.037**	2.81 (0.23 to 5.38)↓↓	**0.033**
ADL independency, S&E	−0.35 (−0.45 to −0.24)↑↑	**<0.001**	−0.35 (−0.46 to −0.24)↑↑	**<0.001**
Dwelling place, home vs. nursing home	4.64 (0.52 to 8.75)↓↓	**0.027**	4.91 (0.70 to 9.13)↓↓	**0.022**
Partner, yes	2.22 (−1.24 to 5.68)	0.208	2.21 (−1.48 to 5.91)	0.239
Motor function, UPDRS III	0.36 (0.26 to 0.47)↓↓	**<0.001**	0.36 (0.26 to 0.47)↓↓	**<0.001**
NMS, NMSS domains				
Cardiovascular including falls	0.47 (0.11 to 0.82)↓↓	**0.010**	0.47 (0.11 to 0.82)↓↓	**0.011**
Sleep/fatigue	0.47 (0.32, 0.63)↓↓	**<0.001**	0.48 (0.33 to 0.64)↓↓	**<0.001**
Mood/apathy	0.52 (0.42 to 0.62)↓↓	**<0.001**	0.53 (0.43 to 0.63)↓↓	**<0.001**
Perceptual problems/hallucinations	0.53 (0.24 to 0.82)↓↓	**<0.001**	0.53 (0.24 to 0.82)↓↓	**0.001**
Attention/memory	0.67 (0.50 to 0.84)↓↓	**<0.001**	0.68 (0.51 to 0.85)↓↓	**<0.001**
Gastrointestinal tract	0.57 (0.37 to 0.78)↓↓	**<0.001**	0.57 (0.37 to 0.78)↓↓	**<0.001**
Urinary	0.23 (0.09 to 0.36)↓↓	**0.001**	0.23 (0.10 to 0.37)↓↓	**0.001**
Sexual function	0.40 (0.23 to 0.56)↓↓	**<0.001**	0.40 (0.23 to 0.57)↓↓	**<0.001**
Miscellaneous[a]	0.35 (0.18 to 0.53)↓↓	**<0.001**	0.36 (0.19 to 0.54)↓↓	**<0.001**
Physician for PD				
PD-specialist[b]	−4.33 (−8.51 to −0.16)↑↑	**0.042**	−3.67 (−8.59 to 1.26)	0.144
Contact for PD, past 3 mo				
PDspecialist	1.25 (−2.22 to 4.71)	0.480	1.26 (−2.23 to 4.76)	0.477
GP	−0.60 (−4.08 to 2.89)	0.737	−0.60 (−4.10 to 2.91)	0.738
PDnurse	−8.48 (−13.09 to −3.86)↑↑	**<0.001**	−8.54 (−13.18 to −3.89)↑↑	**<0.001**
Physiotherapist	6.20 (2.76 to 9.64)↓↓	**<0.001**	6.42 (2.92 to 9.93)↓↓	**<0.001**
Occupational therapist	4.59 (0.03 to 9.14)↓↓	**0.048**	4.63 (0.04 to 9.22)↓↓	**0.048**
Speech/language therapist	4.19 (−0.01 to 8.39)	0.051	4.27 (0.02 to 8.53)↓↓	**0.049**
Hospital admitted	4.10 (0.19 to 8.01)↓↓	**0.040**	4.19 (0.23 to 8.15)↓↓	**0.038**
Rehabilitation admitted	1.18 (−6.25 to 8.62)	0.754	1.22 (−6.29 to 8.72)	0.750
Rehabilitation outpatient	−0.27 (−10.39 to 9.85)	0.958	−0.26 (−10.45 to 9.92)	0.960

↓↓indicates reduced QoL; ↑↑indicates improved QoL. Bold P values are statistically significant at $P < 0.05$. PDQ-8 score range 0–32, higher = worse. HY score range I to V, higher = worse. S&E ADL scale score range 0 to 100, higher = better. UPDRS III score range 0 to 108, higher = worse. NMSS score range 0 to 360, higher = worse.
[a]Miscellaneous domain includes pain, change in ability to taste or smell, change in weight, and excessive sweating.
[b]Neurologist/geriatrician/elderly care physician compared with GP.
PDQ-8, 8-item PD Questionnaire; CI, confidence interval; PD, Parkinson's disease; HY, Hoehn and Yahr staging scale; ADL, activities of daily living; S&E, Schwab & England ADL scale; UPDRS III, Unified PD Rating Scale, Part III, motor examination; NMS, non-motor symptoms; NMSS, Non-Motor Symptoms Scale; GP, general practitioner; Qol, quality of life.

TABLE 3 Multivariable linear regression analyses with PDQ-8 as the dependent variable (n = 354)

Independent Variables*	Unstandardized Coefficient β (95% CI)	Standardized Coefficient β	P Value
Motor function, UPDRS III	0.22 (0.12 to 0.31)↓↓	0.193	**<0.001**
Mood/apathy, NMSS D3	0.29 (0.18 to 0.41)↓↓	0.258	**<0.001**
Attention/memory, NMSS D5	0.27 (0.10 to 0.44)↓↓	0.148	**0.002**
Gastrointestinal tract, NMSS D6	0.27 (0.08 to 0.46)↓↓	0.128	**0.005**
Sleep/fatigue, NMSS D2	0.21 (0.06 to 0.36)↓↓	0.130	**0.007**
Dwelling place, home vs. nursing home	4.58 (0.97 to 8.19)↓↓	0.108	**0.013**
PD nurse past 3 mo	−4.42 (−8.26 to −0.58)↑↑	−0.098	**0.024**
Physiotherapist past 3 mo	3.04 (0.13 to 5.94)↓↓	0.089	**0.040**

↓↓indicates reduced QoL; ↑↑indicates improved QoL. Bold P values are statistically significant at $P < 0.05$. Adjusted R^2 = 0.359. PDQ-8 score range 0 to 32, higher = worse. UPDRS III score range 0 to 108, higher = worse. NMSS score range 0 to 360, higher = worse.
*Independent variables entered in the multivariable linear regression model (backward method): disease severity (HY), ADL independency (S&E), dwelling place (home vs. nursing home), partner, motor function (UPDRS III), NMSS domains 1 to 9, PD specialist (vs. GP), PD nurse past 3 months, physiotherapist past 3 months, occupational therapist past 3 months, speech and language therapist past 3 months, and hospital admitted past 3 months.
PDQ-8, 8-item PD Questionnaire; UPDRS III, Unified PD Rating Scale, Part III, motor examination; NMSS, Non-Motor Symptoms Scale; D, domain; PD, Parkinson's disease; HY, Hoehn and Yahr staging scale; ADL, activities of daily living; S&E, Schwab & England ADL scale; GP, general practitioner; Qol, quality of life.

76 (70–81) years and the median (q1–q3) disease duration was 14 (10–19) years. The majority (262; 66%) of the patients had a partner; 323 (81%) of the patients lived in ordinary housing, and

78 (19%) lived in a nursing home. The median (q1–q3) UPDRS III score was 41 (32–54), the median (q1–q3) NMSS score was 87 (56–122), the median (q1–q3) MMSE score was 26 (24–28),

and the median (q1–q3) GDS-15 score was 6 (4–9). The median (q1–q3) LEDD was 825 (550–1195) mg. The median (q1–13) PDQ-8 score was 44 (34–56) (Table 1).

In the simple linear regression analyses, better HRQoL (PDQ-8) was associated with greater independence in ADL (Schwab & England), living at home, a less severe disease stage (HY), better motor function (UPDRS III), lower NMSS scores in all domains, including less severe cardiovascular, sleep/fatigue, mood, hallucinations, attention/memory, gastrointestinal, urinary ,sexual function , and miscellaneous NMS domain scores (miscellaneous NMSS domain includes pain, change in ability to taste or smell, change in weight, and excessive sweating). Moreover, having a PDspecialist as physician for PD, having had contact with a PDnurse during the past 3 months, and not having had any hospital admissions during the past 3 months were associated with better HRQoL, whereas contact with a physiotherapist or occupational therapist during the past 3 months was associated with worse HRQoL (Table 2). A further characterization of patients who had seen a physiotherapist during the past 3 months indicated that they had considerably more NMS, particularly in the areas of sleep/fatigue and mood/apathy, compared with those who had not seen a physiotherapist. When controlling for NMS using the NMSS, there was no longer a significant relationship of HRQoL with having seen a physiotherapist or occupational therapist, but the relationship with having a PDspecialist or having seen a PDnurse remained.

The multivariable analyses identified better UPDRS III motor function; lower NMSS scores in the domains of mood, attention/memory, gastrointestinal, and sleep/fatigue; living at home; and having seen a PD nurse in the past 3 months as being associated with better HRQoL (PDQ-8) scores. Contact with a physiotherapist during the past 3 months was associated with worse HRQoL (Table 3).

Discussion

This study from the European multicenter CLaSP project is the first to examine HRQoL in a large cohort of patients with late-stage PD, a vulnerable and very disabled patient group that has thus far received little attention in the literature. The results will contribute to the construction of a knowledge base for future research to help improve HRQoL in these severely afflicted patients.

The clinical PD features of non-motor (NMSS) and motor (UPDRS III) symptomatology both had strong negative associations with HRQoL. This underlines the fact that the foundation for improving HRQoL in late-stage PD involves optimizing the treatment for motor and NMS.[5,6,22]

Previous studies have shown that NMS are common in late-stage PD[6,23] and that they generally have a greater impact on HRQoL in PD than motor symptoms.[24–26] The literature provides particularly strong evidence for an association between depressive symptoms and reduced HRQoL in PD.[7,27–32] The

present analyses showed that these negative associations between HRQoL and NMS and particularly depressive symptoms continue to be strong in late-stage PD.

In the univariate analysis of the main sample, we also found that greater independence in ADL was associated with better HRQoL, which is in line with previous research in PD[26] and in the general population.[33,34] Similarly, general self-efficacy has a strong association with life satisfaction in PD.[7]

We furthermore investigated the associations between specific health care factors and HRQoL. Residing at home was associated with a better HRQoL than residing in a nursing home, similar to what has been found in non-PD populations.[35] It was reassuring to find that having recently seen a PD nurse (perhaps reflective of regular reviews) was associated with better HRQoL in a univariate analysis and was among the predictors of the HRQoL scores in the multivariable model. We also found that being followed by a PD specialist was associated with better HRQoL scores in univariate analysis. Previous research also reported that PD specialist care is associated with improved clinical outcomes and greater survival.[36] Having had a recent hospital admission was associated with worse HRQoL; whether this was a causal relationship or merely an association cannot be determined from cross-sectional analysis, although it seems likely that having to be admitted to hospital is probably indicative of a more severe disease and overall health and thereby likely also of a poorer QoL. In addition, we found that having seen a physiotherapist or occupational therapist during the past 3 months was associated with worse HRQoL, which we believe is likely to reflect referral of patients with worse overall functioning to this service. This was also suggested by the finding of a higher rate of NMS, particularly in the areas of sleep/fatigue and mood/apathy, in those who had seen a physiotherapist compared with those who had not seen a physiotherapist. When controlling for NMS, the negative association of having seen a physiotherapist or occupational therapist was no longer observed, although the negative association with having seen a physiotherapist persisted in the overall multivariable analysis. It is likely that patients referred to physiotherapy differed in a number of factors affecting the patients' HRQoL, not all of which we could assess and control for. Motor severity, as assessed by the UPDRS III, was not different between those who had and had not seen a physiotherapist, but as motor severity was high in almost all of the patients, this provided limited information. However, it is likely that patients who experience symptoms that are difficult to treat are referred to physiotherapy, whereas those who are better functioning are not. There is considerable evidence in the literature that physiotherapy is beneficial for the PD population and is essential for maintaining physical function.[37,38] We therefore believe that those referred to physiotherapy represent the most severely affected group and that rather than suggesting that physiotherapy has a negative effect in late-stage PD, the referrals were being made because of the associated severe disability. Worse HRQoL in those who had recently seen a physiotherapist or occupational therapist may also reflect referral based on factors not measured in this study.

Nevertheless, this association will need to be examined in prospective studies in matched samples.

Overall, the percentage of scores explained by the variables examined here was 36%. Aspects of life other than those covered by the questionnaires may also affect a person's HRQoL. Intrinsic factors such as resilience, sense of coherence,[39] and general self-efficacy,[7] which we did not measure in this study, may also be relevant explanatory factors, important for the individual capacity to cope with difficult situations. To support patients adequately for an enhanced HRQoL in late-stage PD, it is likely that individual solutions and resources from a broad spectrum of instances are needed when it comes to both PD-specific and more general health care, including municipality-based health and social care services.

Strengths, Limitations, and Future Perspectives

Across 6 European countries, we successfully included 401 patients in the late and most severe stage of the disease, collecting a substantial amount of information in an area where knowledge was previously limited.[3] As many patients in late-stage PD have considerable difficulties coming to the clinics, we accomplished the inclusion of a high number of participants through a multipronged approach with substantial resource use and often several home visits. Nevertheless, the severity of impairment resulted in some incomplete data with a reduction of the number of participants in the multivariable analysis.

Future studies should continue to investigate and elucidate the symptomatology and the needs of late-stage PD, in order to build a platform of knowledge on which both future research and clinical recommendations can be based. Furthermore, because of the cross-sectional study design, this study cannot provide information on causality. Longitudinal analyses as well as randomized controlled trials will be needed to provide information on the effect of various health care resources and specific treatments.

The results emphasize the importance of optimizing treatment for motor and the range of NMS to improve HRQoL in patients with late-stage PD. PD-specific health care resources, particularly PD nurses, are likely important in addressing issues to improve HRQoL in this population.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

K.R.: 1B, 1C, 2A, 2B, 3A
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S.L.: 1A, 1B, 1C, 3B
W.G.M.: 1A, 1B, 1C, 3B
B.R.B.: 1A, 1B, 1C, 3B
J.J.F.: 1A, 1B, 1C, 3B
R.D.: 1A, 1B, 1C, 3B
A.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3B

Disclosures

Ethical Compliance Statement: The study was approved by the ethical review committees of all participating study centers (London: Camden and Islington National Research Ethics Service (NRES) Committee 14/LO/0612; Bordeaux: South West France and Overseas ethics protection committee III 2014/85; Lisbon: Centro Hospitalar Lisboa Norte, DIRCLN-19SET2014-275; Lund: The Swedish Ethical Review Authority, Joint Programme - Neurodegenerative Disease Research (JPND) HC 559-002; Marburg: Ethics Commission at the State Medical Association Hesse, MC 309/2014; Munich: ethics committee at the Ludwig Maximilian University of Munich (LMU), 193-14; Nijmegen: Radboud University Medical Center, group staff quality and safety human research committee, Arnhem-Nijmegen region, DJ/CMO300). Written informed consent was obtained by the participants. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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