Acta Neurologica Belgica (2018) 118:445–450
https://doi.org/10.1007/s13760-018-0947-3

ORIGINAL ARTICLE

Sensory neuropathic symptoms in idiopathic Parkinson's disease: prevalence and impact on quality of life

Joy K. Adewusi[1] · Marios Hadjivassiliou[2] · Ana Vinagre-Aragón[2] · Karen Ruth O'Connor[2,3] · Aijaz Khan[2] · Richard Adam Grünewald[2] · Panagiotis Zis[2]

Received: 6 March 2018 / Accepted: 16 May 2018 / Published online: 23 May 2018

Abstract

Background Neuropathic symptoms are commonly reported in Parkinson's disease (PD), but robust data on the epidemiology of such symptoms are lacking. The present study sought to investigate the prevalence and determinants of peripheral sensory neuropathic symptoms (PSNS) in idiopathic PD (IPD) and ascertain the effects of such symptoms on the patients' quality of life (QoL).

Methods Patients with IPD and age-matched and gender-matched controls were screened for neuropathic symptoms using the Michigan Neuropathy Screening Instrument. The impact of neuropathic symptoms on QoL was investigated using the 36-Item Short Form Survey.

Results Fifty-two patients and 52 age-matched and gender-matched controls were recruited. PSNS were reported more frequently in patients with IPD than in the control subjects (57.7 versus 28.8%, $p=0.003$). No significant relationships were found between PD-related clinical characteristics (i.e. disease severity and duration, duration of exposure to levodopa) and the presence of PSNS. Significant correlations were found between the number of PSNS and physical functioning (Spearman's Rho −0.351), even after adjusting for age, gender and Hoehn and Yahr score.

Conclusion Our results support the notion of a greater prevalence of PSNS in IPD patients as compared to the general population, which, at least in part, may be secondary to large and/or small fibre peripheral neuropathy. This warrants further investigation in larger studies that include detailed neurophysiological assessments.

Keywords Idiopathic Parkinson's disease · Neuropathic symptoms · Non-motor symptoms · Peripheral neuropathy · Quality of life

Introduction

Peripheral neuropathic symptoms (PNS) usually arise from lesions of the peripheral nervous system. Peripheral nerve disorders can involve different types of nerve fibres and determine the type of neuropathic symptom experienced. For example, damage to small fibres (Aδ and C fibres) can give rise to burning pain, and/or dysautonomia [1, 2]. Large fibre (Aα and Aβ) involvement leads to tingling and loss of pinprick and vibration sensation. When motor fibres are affected, weakness may also manifest [3]. A particularly debilitating peripheral neuropathic symptom is pain, which can occur in both small and large fibre neuropathies. The pain is often described as burning and can be often accompanied by sharp, aching, lancinating sensations particularly of the limbs, most commonly distally [4].

Idiopathic Parkinson's disease (IPD) has a range of cardinal motor and non-motor symptoms (NMS) that often progress in parallel [5–9]. Possible involvement of the small and large nerve fibres can lead to some of the NMS in IPD, such as orthostatic hypotension, urinary difficulties (autonomic dysfunction) and sensory abnormalities such as paraesthesias and pain. These symptoms compound the

✉ Panagiotis Zis
takiszis@gmail.com

[1] Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK

[2] Academic Department of Neurosciences, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Glossop Rd, Sheffield, South Yorkshire S10 2JF, UK

[3] Sheffield Health and Social Care NHS Foundation Trust, Sheffield, UK

disease burden in IPD and have been found to contribute substantially to quality of life (QoL) decline and perhaps to a greater extent than motor symptoms [10–13]. Such symptoms may receive scant attention in movement disorders clinics where treatment response concentrates primarily on motor symptoms.

This study aimed to describe the prevalence of the peripheral sensory neuropathic symptoms (PSNS) in IPD patients as compared with control subjects without IPD, to identify determinants of such symptoms and investigate their overall impact on patient QoL.

Methods

This was a prospective, single centre, case-controlled, cross-sectional study of consecutive patients with IPD attending a dedicated movement disorders clinic.

Study group

Patients with clinically diagnosed Idiopathic Parkinson's disease meeting the relevant diagnostic criteria [14] were identified and recruited from a tertiary Movement Disorder Clinic at the Sheffield Teaching Hospitals NHS Trust. Individuals without IPD were also invited to participate in the study to form an age-matched and sex-matched control group.

All patients and controls provided informed consent for participation. Ethical approval for the identification and recruitment of such patients was received from the NHS Health Research Authority (IRAS220562), and the University of Sheffield institutional ethics review board.

Data collection

For patients with IPD; demographic data, the age at PD symptom onset, age at diagnosis, and start date of levodopa therapy were obtained. Reviews of patient drug charts and clinical notes were conducted to calculate the total cumulative levodopa dose each patient had received from initiation and the duration of use. The current medication regime for PD including dosage was also recorded. A levodopa equivalent daily dose (LEDD) was calculated for each PD patient at the time of recruitment using standardised levodopa formulae as described by Tomlinson et al. [15]. This comprised the patients' daily dose of anti-parkinsonian drugs converted into a subtotal levodopa equivalent dose by the respective drug conversion factor. The individual subtotal levodopa equivalent doses were summed to give the total LEDD. A retrospective drug chart and clinical notes review was performed in order to calculate the total cumulative levodopa each patient had over the years.

Hoehn and Yahr (H&Y) score was given for each IPD patient. The H&Y scale is an assessment scale validated for PD, used to compare groups of patients and provide gross assessment of disease progression [16, 17].

A history of possible risk factors and co-morbidities that could contribute to the presence or development of neuropathic symptoms was elicited from both PD patients and healthy control participants. Subjects with personal and family history of neuropathy, diabetes, thyroid disease, cancer, coeliac disease/gluten sensitivity and excessive alcohol consumption were excluded from this study.

The 36-Item Short Form Survey (SF-36), a self-reported measure of health status and quality of life [18–20], was used to determine patient health-related quality of life by scoring across eight health and QoL concepts over the preceding 4 weeks. These domains include physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health. Each item is measured using a Likert-type scale. Scores were converted and analysed according to the procedure for the SF-36 [21], such that higher scores (out of a total of 100 for each domain) constitute better health-related quality of life in this domain.

The 15-item medical history questionnaire of the Michigan Neuropathy Screening Instrument (MNSI), self-completed by patients, was used to assess the presence and nature of PSNS [22]. The MNSI is used widely for the evaluation of distal symmetrical peripheral neuropathy and has two parts: a 15-item questionnaire and a lower extremity examination that includes inspection and assessment of vibratory sensation and ankle reflexes [22]. The two parts can be used separately as they show similar abilities in predicting confirmed clinical neuropathy (area under the receiver operating characteristic curve is 0.73 for the questionnaire and 0.76 for the examination) [23]. For the analysis we excluded the MNSI items that are not specific to peripheral nerve fibre involvement, such as Item 10 (Do your legs hurt when you walk?). We included the following six PSNS: numbness (Item 1, "Are your legs and/or feet numb?"), burning pain (Item 2, "Do you ever have any burning pain in your legs and/or feet?"), hypersensitivity (Item 3, "Are your feet too sensitive to touch?"), tingling (Item 5, "Do you ever have any prickling feelings in your legs or feet?"), allodynia (Item 6, "Does it hurt when the bedcovers touch your skin?") and temperature sensation (Item 7, "When you get into the bath or shower, are you able to tell the hot water from the cold water?").

Statistical analyses

Data from individual participants were statistically analysed via the Statistical Package for the Social Sciences (SPSS Statistics, version 23).

Frequencies and descriptive statistics were examined for each variable. Comparisons between PD patients and healthy controls were made using Mann–Whitney's *U* test for non-parametric continuous data, Student's *t* test for parametric continuous data and Chi square or Fisher's exact test for categorical data. Correlations between SF-36 domain scores, and total number of neuropathic symptoms were examined using Spearman's correlations. Spearman's Rho values below 0.30 were interpreted as showing a weak correlation, between 0.30 and 0.59 as showing a moderate correlation and values above 0.60 as showing a strong correlation [24].

Where statistically significant correlations or differences were found, these variables were entered into a multiple linear regression model in order to examine the relationships between these independent variables and the SF-36 domain scores (set as the continuous dependent variable).

The level of statistical significance was set at 0.05.

Results

Study population

Fifty-two patients with IPD and 52 age-matched and gender-matched controls were recruited. Table 1 summarises the demographic characteristics of the two groups.

For the clinical characteristics of the PD group, mean duration of disease was 8.6 ± 5.9 years (range 2–27 years). Both mean H&Y score was 2.0 ± 0.8 (median 2.0, interquartile range 1.5–2.5). The mean duration of treatment with levodopa, was 6.4 ± 5.6 years (range 1–26 years). The mean current LEDD was measured at 839.0 ± 508.1 mg, while the mean cumulated levodopa dose for the group was 1.02 ± 1.33 kg.

Neuropathic symptoms in IPD patients and healthy control participants

As shown in Table 1, IPD patients reported higher total number of neuropathic symptoms as compared to controls (1.1 ± 1.3 versus 0.5 ± 0.8, $p = 0.003$). In total, 57.7% of PD patients experienced at least 1 PSNS as compared to 28.8% in the control group ($p = 0.003$). PD patients experienced

Table 1 Demographic data, the presence of PSNS and quality of life in PD patients and healthy control participants

	PD patients ($n = 52$)	Healthy controls ($n = 52$)	p value*
Demographics			
Age, in years (SD)	68.1 (8.4)	66.8 (10.0)	0.480
Male gender (%)	38 (73.1)	38 (73.1)	1.000
PSNS			
Numbness (%)	14 (26.9)	4 (7.7)	0.010
Burning pain (%)	12 (23.1)	4 (7.7)	0.030
Hypersensitivity (%)	8 (15.4)	1 (1.9)	0.031
Tingling (%)	17 (32.7)	9 (17.3)	0.070
Allodynia (%)	4 (7.7)	3 (5.8)	0.696
Loss of temperature sensation (%)	2 (3.8)	3 (5.8)	0.647
At least 1 PSNS (%)	30 (57.7)	15 (28.8)	0.003
Total number of PSNS (%)	1.1 (1.3)	0.5 (0.8)	0.003
Quality of life			
Physical functioning, mean score (SD)	49.2 (26.6)	77.9 (23.2)	< 0.001
Physical role limitations, mean score (SD)	40.7 (31.2)	77.0 (25.9)	< 0.001
Emotional role limitations, mean score (SD)	61.2 (36.0)	83.0 (25.6)	0.001
Energy/fatigue (vitality), mean score (SD)	42.2 (18.8)	56.3 (20.3)	< 0.001
Emotional well-being, mean score (SD)	63.2 (22.8)	73.8 (16.7)	0.008
Social role, mean score (SD)	50.7 (28.8)	78.8 (26.0)	< 0.001
Bodily pain, mean score (SD)	48.1 (31.3)	68.5 (27.6)	0.001
General health perceptions, mean score (SD)	35.7 (19.1)	64.0 (20.1)	< 0.001
Perceived health change, mean score (SD)	38.0 (21.9)	49.0 (18.5)	0.006

PD Parkinson's disease, *PSNS* peripheral sensory neuropathic symptoms, *SD* standard deviation

numbness, burning pain and hypersensitivity more than controls. The two groups, however, did not differ significantly in symptoms of allodynia, tingling and loss of temperature sensation. The total number of PSNS did not differ significantly between male and female patients (1.2 ± 1.4 versus 0.9 ± 0.9, respectively, $p = 0.565$). No significant correlation between the total number of PSNS and the patient's age was observed (Spearman's Rho -0.007, $p = 0.963$), or the total number of PSNS and the H&Y score (Spearman's Rho 0.161, $p = 0.254$).

Quality of life in IPD patients and healthy control participants

Table 1 also summarises the quality of life measures assessed with the SF-36 survey in both groups. As expected, there was a significant difference between the control group and the IPD group across all QOL measures. PD patients had lower scores, reflecting an impaired quality of life in PD patients.

PD-related clinical characteristics and neuropathic symptoms

IPD patients with and without neuropathic symptoms did not differ significantly regarding the mean disease duration, disease severity, current LEDD, years of levodopa exposure and cumulated levodopa (Table 2).

Impact of neuropathic symptoms on IPD QoL

Table 3 summarises the correlations between the number of PSNS and the different QoL aspects. Significant correlations were found in physical functioning (Spearman's Rho -0.351).

After adjusting for age, gender and H&Y score, the total number of PSNS was still correlated significantly with the physical functioning score (beta -0.282, $p = 0.034$).

Table 3 Correlations between the burden of PSNS and QoL in PD patients

QoL measures	Total number of PSNS
Physical functioning	
Spearman's Rho	− 0.351
p value	0.011
Physical role limitations	
Spearman's Rho	− 0.189
p value	0.180
Emotional role limitations	
Spearman's Rho	− 0.226
p value	0.108
Energy/fatigue	
Spearman's Rho	− 0.126
p value	0.374
Mental health/emotional well-being	
Spearman's Rho	− 0.104
p value	0.463
Social role	
Spearman's Rho	− 0.121
p value	0.392
Bodily pain	
Spearman's Rho	− 0.069
p value	0.627
General health perceptions	
Spearman's Rho	− 0.223
p value	0.112
Reported change	
Spearman's Rho	− 0.236
p value	0.093

PSNS peripheral sensory neuropathic symptoms, *QoL* quality of life, *PD* Parkinson's disease

Table 2 Clinical characteristics of PD patients with and without peripheral sensory neuropathic symptoms

	Patients with PSNS ($n = 30$)	Patients without PSNS ($n = 22$)	*p* value*
Age, in years (SD)	68.3 (8.8)	67.8 (8.1)	0.830
Male gender (%)	21 (70.0)	17 (77.3)	0.550
PD duration, in years (SD)	9.7 (6.2)	7.2 (5.4)	0.137
H&Y score (SD)	2.2 (0.9)	1.9 (0.6)	0.235
Duration on levodopa, in years (SD)	7.2 (5.7)	5.4 (5.4)	0.259
Current LEDD, in mg (SD)	845.0 (429.7)	830.8 (609.9)	0.922
Cumulated levodopa, in kg (SD)	1.16 (1.11)	0.8 (1.6)	0.406

PD Parkinson's disease, *PSNS* peripheral sensory neuropathic symptoms, *SD* standard deviation, *LEDD* levodopa equivalent daily dose

Discussion

Our study aimed to establish the prevalence of PSNS in a cohort of IPD patients and compare this with age-matched and gender-matched controls without IPD. We also aimed to investigate the effect of such symptoms on the QOL in IPD patients.

The prevalence of neuropathic symptoms in patients with IPD was two times higher when compared to controls. This finding is concordant with a recent meta-analysis that showed the prevalence of PN in IPD to be double that found in the general population [25, 26]. The range of PSNS within our IPD population was wide, however significant differences were found in the specific symptoms of numbness, burning pain and hypersensitivity. The last two symptoms in particular are suggestive of underlying small fibre neuropathy (SFN). It is therefore possible that SFN may be more prevalent in IPD. Such pain is not captured by the King's Parkinson's disease Pain Scale (KPPS), a novel validated questionnaire for pain in PD [27]. The most relevant to SFN question in the KPPS is this of "burning pain associated with oedema or dopaminergic treatment" (domain 6, item 12). However, patients with IPD report burning pain even in the absence of oedema and pain not related to their treatment. Therefore, addition of an 8th domain to the KPPS that will be addressing peripheral neuropathic pain is recommended so to capture patients with SFN, which seems to be prevalent in IPD.

There is no robust evidence supporting any direct association between the development of PN (confirmed neurophysiologically) in IPD and demographic or PD-related characteristics including intrinsic effects of PD treatment. Ceravolo et al. described age and duration of exposure to levodopa as main risk factors for the development of neuropathy in IPD, in a PD population stratified by levodopa exposure [28]. Contrary to this study, several studies found levodopa does not influence the development or progression of PN in IPD. Nolano et al. reported no difference in the fibre density (measured through skin biopsies) between treated and untreated patients [29]. Shahrizaila et al. showed that electro-diagnostic criteria for distal symmetric polyneuropathy were fulfilled in similar proportions of treated and treatment-naïve patients [30] while Rajabally and Martey reported that only age and serum folate concentration correlated with PN in IPD [31].

The present study did not confirm any previously described associations between neuropathy and PD-related characteristics [28–31] as no correlations between the presence of PSNS and the duration of levodopa exposure (years), the duration of disease, the age and the PD severity were found. One of the novelties of our study was that we calculated the cumulative levodopa dose for each of the IPD subjects, which was also found not to correlate with the presence of neuropathic symptoms. The contradicting existing literature is consistent with multifactorial determinants of neuropathic symptoms in PD.

Lower scores on the SF-36 reflect poorer health status and QoL. In our IPD population, the presence of PSNS had a significant impact on the physical functioning as assessed by the SF-36, even after adjusting for age, gender and disease duration. The correlation between QoL measures and physical disability in IPD has been shown previously [32] but the demonstration that PSNS represent a significant burden to patients with IPD is new.

Our findings should be interpreted with some caution given the limitations of our study design. Firstly, the results of the study may be subject to selection bias as it was a single-centre hospital-based study rather than a community based or a multi-centre study. Also some of the measurements (such as the cumulative levodopa) were based on a retrospective review of clinical notes and drug charts and therefore a bias is possible. Although we used a validated tool for capturing a wide range of PSNS, some of the symptoms reported may still not be the result of underlying peripheral neuropathy but of central origin, for example central neuropathic pain due to thalamic impairment. Therefore, we could not provide firm evidence about the presence of a large fibre or a small fibre neuropathy. For this, a further study that incorporates conclusive diagnosis of neuropathy is needed. Such a study should include full neurophysiological assessment for the presence of large fibre peripheral neuropathy and quantitative sensory testing, sudo-motor examination, corneal confocal microscopy and/or a skin biopsy for the assessment of small fibre dysfunction.

In conclusion, our findings suggest a higher prevalence of peripheral sensory neuropathy symptoms in IPD with a significant impact on patients QoL. Precise determinants of such symptoms and possible underlying pathophysiological mechanisms have been suggested, but remain debated in the current literature. No evidence for PD-related risk associations was obtained in this study, highlighting the need for larger scale cohort studies and carefully planned prospective studies with full neurophysiological assessments for peripheral neuropathy.

Acknowledgements This is a summary of independent research supported by BRC and carried out at the National Institute for Health Research (NIHR) Sheffield Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the BRC, NHS, the NIHR or the Department of Health. Dr Zis is sincerely thankful to the Ryder Briggs Fund.

Compliance with ethical standards

Conflict of interest The authors declare no financial or other conflicts of interest.

Ethical approval Ethical approval for the identification and recruitment of such patients was received from the NHS Health Research Authority (IRAS220562), and the University of Sheffield institutional ethics review board.

Informed consent All patients and controls provided informed consent for participation.

References

1. Lacomis D (2002) Small-fiber neuropathy. Muscle Nerve 26:173–188
2. Zis P, Sarrigiannis PG, Rao DG, Hewamadduma C, Hadjivassiliou M (2016) Chronic idiopathic axonal polyneuropathy: a systematic review. J Neurol 263:1903–1910
3. Richardson JK, Hurvitz EA (1995) Peripheral neuropathy: a true risk factor for falls. J Gerontol A Biol Sci Med Sci 50:M211–M215
4. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ (2004) Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med 21:976–982
5. Braak H, Braak E, Yilmazer D, Schultz C, de Vos RA, Jansen EN (1995) Nigral and extranigral pathology in Parkinson's disease. J Neural Transm Suppl 46:15–31
6. Caligiore D, Helmich RC, Hallett M, Moustafa AA, Timmermann L, Toni I, Baldassarre G (2016) Parkinson's disease as a system-level disorder. NPJ Parkinsons Dis 2:16025
7. Jellinger KA (1991) Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. Mol Chem Neuropathol 14:153–197
8. Kalia LV, Lang AE (2015) Parkinson's disease. Lancet 386:896–912
9. Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P (2011) Parkinson's disease: the non-motor issues. Parkinsonism Relat Disord 17:717–723
10. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, NMSS Validation Group (2011) The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord 26:399–406
11. Zis P, Erro R, Walton CC, Sauerbier A, Chaudhuri KR (2015) The range and nature of non-motor symptoms in drug-naive Parkinson's disease patients: a state-of-the-art systematic review. NPJ Parkinsons Dis 1:15013
12. Zis P, Rizos A, Martinez-Martin P, Pal S, Silverdale M, Sharma JC, Sauerbier A, Chaudhuri KR (2014) Non-motor symptoms profile and burden in drug naïve versus long-term Parkinson's disease patients. J Parkinsons Dis 4:541–547
13. Zis P, Martinez-Martin P, Sauerbier A, Rizos A, Sharma JC, Worth PF, Sophia R, Silverdale M, Chaudhuri KR (2015) Non-motor symptoms burden in treated and untreated early Parkinson's disease patients: argument for non-motor subtypes. Eur J Neurol 22:1145–1450
14. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30:1591–1601
15. 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
16. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, Giladi N, Holloway RG, Moore CG, Wenning GK, Yahr MD, Seidl L (2004) Movement Disorder Society Task Force on Rating Scales for Parkinson's disease. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord 19:1020–1028
17. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427–442
18. Hays RD, Shapiro MF (1992) An overview of generic health-related quality of life measures for HIV research. Qual Life Res 1:91–97
19. Stewart AL, Hays RD, Ware JE Jr (1988) The MOS short-form general health survey. Reliability and validity in a patient population. Med Care 26:724–735
20. Stewart JD, Low PA, Fealey RD (1992) Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. Muscle Nerve 15:661–665
21. Hays RD, Sherbourne CD, Mazel RM (1993) The RAND 36-Item Health Survey 1.0. Health Econ 2:217–227
22. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA (1994) A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 17:1281–1289
23. Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary PA, Albers JW, Feldman EL, DCCT/EDIC Research Group (2012) Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabet Med 29:937–944
24. Mukaka MM (2012) Statistics corner: a guide to appropriate use of correlation coefficient in medical research. Malawi Med J 24:69–71
25. Zis P, Grünewald RA, Chaudhuri RK, Hadjivassiliou M (2017) Peripheral neuropathy in idiopathic Parkinson's disease: a systematic review. J Neurol Sci 378:204–209
26. Italian General Practitioner Study Group (IGPSG) (1995) Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions. I. Prevalence and general characteristics of the sample. Neurology 45:1832–1836
27. Chaudhuri KR, Rizos A, Trenkwalder C, Rascol O, Pal S, Martino D, Carroll C, Paviour D, Falup-Pecurariu C, Kessel B, Silverdale M, Todorova A, Sauerbier A, Odin P, Antonini A, Martinez-Martin P, EUROPAR and the IPMDS Non Motor PD Study Group (2015) King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation. Mov Disord 30:1623–1631
28. Ceravolo R, Cossu G, Bandettini di Poggio M, Santoro L, Barone P, Zibetti M, Frosini D, Nicoletti V, Manganelli F, Iodice R, Picillo M, Merola A, Lopiano L, Paribello A, Manca D, Melis M, Marchese R, Borelli P, Mereu A, Contu P, Abbruzzese G, Bonuccelli U (2013) Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study. Mov Disord 28:1391–1397
29. Nolano M, Provitera V, Lanzillo B, Santoro L (2011) Neuropathy in idiopathic Parkinson disease: an iatrogenic problem? Ann Neurol 69:427–428
30. Shahrizaila N, Mahamad UA, Yap AC, Choo YM, Marras C, Lim SY (2013) Is chronic levodopa therapy associated with distal symmetric polyneuropathy in Parkinson's disease? Parkinsonism Relat Disord 19:391–393
31. Rajabally YA, Martey J (2013) Levodopa, vitamins, ageing and the neuropathy of Parkinson's disease. J Neurol 260:2844–2848
32. Ward CD (2000) What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 69:289–290