PERIPHERAL POLYNEUROPATHY IN IDIOPATHIC PARKINSON'S DISEASE WITH ORAL LEVODOPA: PREVALENCE AND ASSOCIATED FACTORS

NEUROPATIA PERIFÉRICA NA DOENÇA DE PARKINSON IDIOPÁTICA COM LEVODOPA ORAL: PREVALÊNCIA E FATORES ASSOCIADOS

Maria das Graças Loureiro C. Campêlo[1,4], Clarissa Loureiro das Chagas Campêlo[2], Jovany Luis A Medeiros[3], Ailton S. Melo[4]

ABSTRACT
Purpose- Identify the prevalence and factors associated with the development of peripheral neuropathy(PN) in idiopatic Parkinson's disease (IPD).Method: 66 subjects (36 Parkinson group and 30 control group) were evaluated using clinical criteria of PN, nerve conduction study (NCS), dosages of VB12, folate, homocysteine, levodopa exposure, duration and severity of IPD. Results: Most individuals had symptoms suggestive of PN that was confirmed in 3(8%) IPD group and 1(3%) control. Homocysteine levels were higher in IPD patients [16.01 ± 6.88; controls 14.68 ± 5.77, p = 0.403], low levels of vitamin B12 were more frequent in controls. There was no association between biochemical measurements, levodopa use and neuropathy. Neuropathy was associated with IPD (RC = 2.64). Conclusion: In this study individuals with IPD had larger neuropathic scores more than controls but neuropathy was only associated with the presence of IPD.138

Keywords: Parkinson's disease; Homocysteine; Levodopa; Neuropathy; Prevalence.

RESUMO
Objetivo: Identificar a prevalência e os fatores associados ao desenvolvimento da neuropatia periférica (NP) na doença de Parkinson idiopática (DPI). Método: 66 indivíduos (36 grupo parkinson e 30 grupo controle) foram avaliados pelos critérios clínicos de NP, pelo estudo da condução nervosa, dosagens de VB12, folato, homocisteina, exposição à levodopa, duração e gravidade da DPI. Resultados:A maioria dos indivíduos apresentava sintomas sugestivos de neuropatia que foi confirmada pelo estudo da condução nervosa em 3(8%) do grupo Parkinson e em 1(3%) do grupo controle. A homocisteina estava mais elevada nos pacientes com DPI [16.01 ± 6.88; controles 14.68 ± 5.77, p = 0.403], níveis mais baixos de VB12 foram mais frequentes nos controles. Conclusão: Neste estudo indivíduos com DPI apresentaram escores neuropáticos mais elevados que os controles, mas a neuropatia periférica esteve associada apenas a presença da DPI.

Palavras-chave: Doença de Parkinson; Homocisteina; Levodopa; Neuropatia; Prevalência.

1 INTRODUCTION

The idiopathic Parkinson's disease (IPD) is the second most frequent neurodegenerative disease[(1)]. The neurodegenerative process affects the striatum and other areas outside the basal ganglia circuit. In recent decades, it has been found that some individuals with IPD may have involvement of peripheral nervous system (PNS)[(2-9)], which aggravates the motor performance of these patients. Such involvement has been documented in some forms of parkinsonism[(10)], in individuals with IPD treated with LD by intestinal

[1,4]Medicine course, Universidade Federal de Campina Grande, Paraíba, Brazil. E-mail: gracas.loureiro@bol.com.br
[2] Programa de pós-graduação em Psicobiologia da Universidade Federal do Rio Grande do Norte
[3] School of Physiotherapy, Universidade Estadual da Paraíba, Campina Grande, Paraíba, Brazil. E-,ail: jovany.medeiros@gmail.com
[4] Postgraduate course in Medicine and Health, Faculdade de Medicina da Universidade Federal da Bahia, Salvador, Bahia, Brazil. E-mail: asm@ufba.br

infusion[11,12] and also in patients treated with oral LD[2-9]. The prevalence of PN is not well defined, some studies have reported prevalence ranging from 10% to 55% [2,3] while others have questioned whether it can really occur[13-15].

There is no consensus on what causes neuropathy in IPD: if it is mere coincidence; if it is a result of treatment with LD, increased homocysteine (Hcy), methylmalonic acid (MMA), lack of vitamin B12 (VB12) that is common in the age group most involved in this disease, or if is a result of the progression of the neurodegenerative process, since it was mainly observed in the later stages of the disease[5,6,11,16] and can affect subjects without LD treatment[5,8,9].

The aim of this study was identify the prevalence of PN in IPD and the factors involved in the neuropathy development, in particular, the role of LD, VB12, folate as well as the Hcy and MMA compared with healthy controls.

2 PATIENTS AND METHODS

Between August 2011 and November 2012, we conducted cross-sectional study involving 36 patients with a diagnosis of IPD according to UK Brain Bank Diagnostic criteria[16] attending at the Neurology Clinical of the Alcides Carneiro University Hospital (HUAC) of the Federal University of Campina Grande (UFCG)-Paraíba-Brazil, and 30 sex and age-matched (± 3 years) healthy controls recruited from two Care station of the Family Health Program in the same city. Individuals of the two groups with a history of other neurological diseases, using amiodarone, metformin, dopamine blockers in the past 12 months, with reports of alcoholism, diabetes, thyroid disease, liver disease, kidney disease and/or cancer were excluded from the study. All participants underwent a questionnaire about epidemiological data, morbid past and possible risk factors to PN.

This study received approval from the Ethical Committee on Human Research of the HUAC- Federal University of Campina Grande (UFCG) Paraíba-Brazil under the number: 20101612-053. A written informed consent was obtained from each participant.

2.1 Parkinson group

The patients were examined by one neurologist, and the clinical data of individuals were assessment through a questionnaire for age at onset symptoms, disease duration and treatment to IPD, daily dose and duration of LD. A complete neurological examination were carried out in all patients and the scales of the Hoehn &Yahr (HY)[17] for disease staging, and

the Unified Parkinson's Disease Rating Scale (UPDRS)[18] for the assessment of daily living activities (UPDRS II) and motor impairment (UPDRS III) were applied during the "on" phase.

2.2 Procedures

Peripheral neuropathy was defined using American Academy of Neurology and Electrodiagnostic Medicine (AANEM) criteria (combination of clinical and nerve conduction study (NCS) findings suggesting the "highest ordinal likelihood" of PN)[19].

Peripheral nerve function was evaluated using the Toronto Clinical Scoring System (TCSS)[20], Neuropathy Symptom Score (NSS) and Neuropathic Disability Score (NDS)[21]. The TCSS is based upon history and examination with emphasis upon sensory deficits, and can be used in assessement of neuropathy of different etiologies. The cutoff score of ≥5 was considered positive for clinical diagnosis of PN [20].

The NSS assesses the number of neurologic symptoms that an individual experiences. The final score ranges from 0 to 9 and allows to classify the symptoms into mild (3 to 4 points), moderate (5 to 6 points) and severe (7 to 9 points) [21]. The NDS assesses neurological signs systematically, assess the ankle tendon reflex, vibratory, painful and thermal sensations of the hallux bilaterally. Sensory modalities are scored with (0) if present, (1) if reduced/absent, and reflections with (0) if normal, (1) if present with reinforcement or (2) if absent, for each side. Score 3 to 5 is considered as evidence of mild neuropathic signals; 6 to 8 as moderate and 9 to 10 as severe neuropathic signals [21].

2.3 Neurophysiological study

The NCS was performed after clinical assessment and before knowledge of the laboratory results using a device Nicolete Biomedical Inc. The examination was performed by a single neurophysiologist blinded to the participants condition - exposure to L-dopa and biochemicals dosages, existence of signs and symptoms of neuropathy. The NCS was conducted in bilateral peroneal and sural nerves following the simplified protocol adopted by the AANEM [19]. The normal values of the parameters evaluated included: to peroneal nerve: distal latency (<5.6 ms), amplitude (> 3mV) and conduction velocity (> 36m/s); to sural nerve: distal latency (<3.6 ms), amplitude (> 6μV) and conduction velocity (> 40m/s). The presence of alterations in at least two parameters and two symmetrical nerves was adopted as a diagnostic criterion for PN.

2.4 Laboratory work-up

VB12, folate, Hcy and MMA were measured in all patients of the two groups. Serum VB12, folate and Hcy levels were measured by chemiluminescence method and MMA was measured in the urine by the method of p-nitroaniline reaction. The normal lower limit for VB12 was 210pg/mL and 3.0ng/mL for folate. The upper limit for Hcy was 12.0 umol/L in adult men, 10.0 umol/L in adult woman. MMA values > 3.2 mmol creatinine in urine was adopted for diagnosis of VB12 deficiency. All the blood samples were collect on the morning following a 12-hour fast and 12 hours off IPD drugs.

To rule out other causes of neuropathy, we also performed in all patients the following exams: complete blood cell count, fasting glucose, liver enzymes, thyroid stimulating hormone, urea, creatinine, cholesterol and triglycerides.

2.5 Statistical Analysis

Statistical analyses were performed by using the statistical package SPSS, version 22.0. Frequencies and quantitative analyses were calculated for categorical and quantitative variables, respectively. We used the independent sample t-test to compare clinical evaluations of the PN, nerve conduction study and biochemical measurements data. The bivariate linear regression test was used to analyze the association between the diagnostic parameters of PN and the use of LD. We used Pearson correlation test to analyze NCS parameters, clinical and biochemical data. P value <0.05 was considered as statistically significant.

3 RESULTS

We screened 71 participants (39 patients with IPD and 32 sex and age-matched healthy controls). Three patients with IPD were subsequently excluded, one because no concluded the laboratorial exams, and two because hematological findings disclosed in one previously unrecognized diabetes and another hypothyroidism. In control group two were excluded because the NCS disclosed compressive neuropathy. Thus 36 patients with IPD (16 men and 20 women) and 30 controls (12 men and 18 women) were included.

3.1 Prevalence of the IPD

The current age of the IPD patients was 68.8±7.8years for men and 69.9±6.1 years for women. In control group, the age was 72.0±6.0 years for men and 69.6±6.1 years for women. Twenty-eight (77%) patients with IPD and 14(46%) controls claimed symptoms suggestive of

PN. All patients with IPD and 22(73%) controls had same clinical findings of PN. Only three patients with IPD and one control fulfilled AANEM criteria for PN, yielding a prevalence of 8% and 3% respectively.

3.2 Clinical features of neuropathy

The installation of signs and/or symptoms suggestive of PN in all IPD patients and controls were reported as insidious and had more than six months of duration.The TCSS/NDS was significantly higher in IPD patients than in controls. The NSS was higher in IPD with borderline significant between groups (Table 1).

The most common symptoms were fatigue and cramping sensations in the lower limbs, in both groups: control group (40%) and IPD (50%). There was predominance of alterations in ankle tendon reflex (66.7% in the control group and 72.3% in the IPD group [t (64) = -1.97, p = 0.052)] and vibratory sensitivity (56.7% in the control group and 69.4% in the IPD group [t (64) = -2.78, p <0.05)].

Table 1 - Data from the clinical evaluation of peripheral neuropathy by the scores of Toronto, Symptoms and Neuropathic Impairment

		Control group		IPD[a] Group		p
		M±SD[b]	**n (%)**	**M±SD**	**n (%)**	
TCSS[c]		**3.8± 2.6**		**5.3±1.8**		**0.012***
	Without PN[d]		16 (53.3)		14 (38.9)	
	With PN		14 (46.7)		22 (61.0)	
NSS[e]		**3.4±2.4**		**4.4±1.6**		**0.052**
	No symptoms		10 (33.3)		5 (13.3)	
	Mild		9 (30.0)		11 (30.6)	
	Moderate		8 (26.7)		17(47.2)	
	Severe		3 (10.0)		3 (8.3)	
NDS[f]		**3.0±2.3**		**4.2±1.7**		**0.026***
	No signals		12 (40.0)		7 (19.4)	
	Mild		14 (46.7)		19 (52.8)	
	Moderate		3 (10.0)		10 (27.8)	
	Severe		1 (3.3)		-	

a.Idiopatic Parkinson disease; b. M = Mean, SD = standard deviation; c.TCSS= Toronto Clinical System Score; d. PN= Peripheral neuropathy; e. NSS = Neuropathic Symptoms Score; f. NDS = Neuropathy Disability Score. (*p <0.05 obtained by the t-test for independent samples).

3.3 Levodopa dose, duration of exposure and others therapies

The duration of treatment for IPD ranged from one to 12 years (5.7 ± 2.9 years), 52.7% of patients were in stages 2 and 2.5 of HY scale and the score of UPDRS III was 32.6±15.7 for men and 30.6±12.8 for women (range 10-74). The disease duration was 6.0 ± 2.5 years for women and 5.5 ± 3.4 years for men. Thirty-three (91.7%) of patients were using LD, 25 (69.4%) on >400mg of LD for at least the last four years. Dose of LD ranged from 375mg to 1,500mg/day (600.0±366.6). Same patients were taking others antiparkinsoniam drugs: 30.5% amantadina (dose ranged from 150 to 300mg/day), 19.4% pramipexol (dose ranged from 0.325 to 1.5mg/day) and 16.6% biperideno (dose ranged from 2-6mg/day). No one patients was taking COMT inhibitors. No subject in the two groups were taking any vitamin supplementation.

The dose, time of exposure to LD, severity of IPD impairment and the neuropatic scores in the three patients with IPD and peripheral neuropathy are in (Table 2).

Table 2 - Dose, time of exposure to levodopa, severity of the disease and neuropathic characteristics of the three patients with IPD and neuropathy

Patient	gender	age	Duration of PD	Time of exposure to LD	LD dose	HY	UPDRS III	TCSS	NSS	NDS
1	M	72	12	12	750	4.0	66	8	7	6
2	F	70	8	-	-	3.0	31	7	6	6
3	F	61	5	4	750	2.0	27	6	4	4

M-men; F-female; IPD-Idiopatic Parkinson disease; LD- levodopa; HY-Hoehn and Yahr; UPDRS-Unified Parkinson Disease Rathing Scale; TCSS-Toronto score; NSS-Neuropathic Symptoms Score; NDS-Neuropathic Disability Score

3.4 Laboratory data

The routine biochemical screening were normal in all patients. Hcy levels were elevated in both groups (73.3% of controls and 80.6% of IPD) and the levels of VB12 (30% of controls and 19.4% of IPD) were reduced. No changes in the levels of folate were found. Measurement of MMA in urine was negative in all participants. No significant statistical differences were detected by the independent samples T-test for all substances assayed (Table 3). Likewise, no statistical difference was found between participants of IPD group with and without PN (Table 4).

Table 3 - Comparasion of the levels of homocysteine, vitamin B12, folate between individuals with IPD and control group

Variable	Control group	IPD[a] group	P
Hcy[b] mean±SD (µmol/L)	14.68 ± 5.77	16.01 ± 6.88	0.403
VB12[c] mean±SD (pg/mL)	331.61 ± 213.17	343.52 ±165.15	0.961
Folate mean±SD[d] (ng/mL)	10.57 ± 3.86	10.51 ± 5.48	0.799

a.IPD = Idiopathic Parkinson's Disease; b. Hcy: homocysteine; c.VB12: vitamin B 12; d.Standard Deviation. Values expressed as mean and standard deviation (p value by the t- test for independent samples).

Table 4 - Comparasion of the levels of homocysteine, vitamin B12, folate between individuals with IPD with and without PN.

Variable	IPD[a] with PN[b]	IPD without PN	P
Hcy[c] mean±SD (µmol/L)	15.3 ± 3.0	15.4 ± 6.5	0.137
VB12[d] mean±SD (pg/mL)	298.2 ± 64..98	341.2 ±192.1	0.099
Folate mean±SD[e] (ng/mL)	11.8 ± 6.0	10.4 ± 4.7	0.579

a.IPD = Idiopathic Parkinson's Disease; b.PN=peripheral polyneuropathy; c. Hcy: homocysteine; d.VB12: vitamin B 12; e. Standard Deviation. Values expressed as mean and standard deviation (p value by the t- test for independent samples).

3.5 Neurophysiological findings

The nervous conduction study confirmed the presence of PN in three individuals of IPD group (8%), and in one individual of the control group (3%). Significant reduction of amplitude of peroneal nerves was observed in IPD group (the right ($t(64)=3.24, p<0.005$) and left ($t(64=0.33, p<0.05$) (Table5)

Table 5 - Data from NCS parameters for the control and Parkinson groups.

		Reference value	Control group	IPD[a] group	p
Sensory study	DSL[b]	<3.6	2.46±0.38	2.50±0.43	0.717
Sural	Amplitude (µV)	>6.0	10.90±5.21	10.47±3.57	0.695
	Velocity (m/s)	>40	47.58±7.13	45.37±8.79	0.273
Motor study	DML[c]	<5.6	4.35±0.94	4.52±0.62	0.361
Peroneal	Amplitude (mV)	>3.0	7.07±2.57	5.27±2.05	**0.002***
	Velocity (m/s)	>36	45.61±3.75	45.11±3.19	0.557

a.IPD: Idiopatic Parkinson's Disease; DSL: b.Distal sensory latency; c.DML: Distal motor latency. Values expressed as mean and standard deviation (p values were obtainedby independent samples t-test).

For IPD group, correlation analysis to neurophatic scores (TCSS, NSS, NDS), clinical evaluations (UPDRS, HY), Hcy, VB12 levels and NCS parameters showed negative correlation between amplitude of the peroneal nerve and HY ($r = -0.337$, $p < 0.05$) and NSS ($r = -0.398$ $p < 0.05$) scores. For the control group, no significant results were found for the same correlation analysis.

The NCS data showed a mismatch between the PN diagnosis by the TCSS and the NCS results. In the same way, the regression test indicated no association between the TCSS and the PN diagnosis in the sample studied (phi = 023). Also, there was no association between the use of LD and neuropathy onset (phi = 0.533).

The measure of association between the results of NCS and values of biochemical analysis showed no association between levels of Hcy, VB12, folate and PN diagnosis (coef. association= 0.30). Only the presence of IPD was associated with the PN development (RC = 2.64), indicating a greater chance of developing PN in patients with IPD (Table 6).

Table 6 - Comparison of measures of association between nervous conduction study, biochemical dosages and Parkinson's disease

Variable	Coef. c	Coef. 001T	phi	RR	RC	pQui	Applicable
Group IPD[a]	0.104	0.104	0.104	2.52	2.64	0.40	-1
Hcy[b]	0.104	0.014	-0.014	0.88	0.88	0.91	-1
Folate	0.032	0.032	-0.032	0.00	0.00	0.80	-1
VB12[c]	0.14	0.144	-0.144	0.0	0.00	0.24	-1

a.IPD=Idiopatic Parkinson's disease; b. Hcy = Homocysteine ; c.VB12 = Vitamin B12; d. NCS = nervous conduction study. Univariate analysis between NCS[d] and Hcy, folate, VB12 and Parkinson's disease.

4 DISCUSSION

In recent decades, studies has been reported prevalence of 10% to 55% of PN in patients with IPD[2-4]. Prolonged exposure to high doses of LD has been identified as the cause of the neuropathy[2-4], but some studies questioning this association[13-15] and others factors, such us IPD by itself should be considered an important risk factor for neuropathy [6,15].

Our data showed that neuropathy can affect individuals with IPD although the prevalence in the studied group has not been so high. Theses results are in agreement with those obtained by same researchers[2-4,6] which show that peripheral neuropathy can affect

individuals with IPD treated with oral LD and that frequency is higher in the IPD group than in controls, particularly in moderate and advanced phase of disease[6,8,9].

In our study, the presence of neuropathic symptoms and sings in most participants and, the diagnostic confirmation of PN by NCS only in three individuals with IPD and one control showed discordance between clinical and neurophysiological criteria for neuropathy which can be partly explained by the age of the participants, who mostly were over 60 years old. These parameters may change with aging, not meaning neuropathy by itself [23]. Furthermore, some symptoms suggestive of PN (pain, weakness, cramps) can result of other cause. Another reason for is that electroneuromyography has greater sensitivity and specificity in confirming the impairment of large fibers, however, the involvement of fine fibers sometimes cannot be diagnosed by this method[24] .

The prolonged use of high doses of LD is suggested as a possible factor for the PN development in IPD. It would lead to hyperhomocysteinemy (HHcy) and VB12 deficiency[2-4,7]. This vitamin acts as important cofactor in the remethylation reaction of Hcy and may suffer decreased by greater use during this reaction, favoring the formation of its metabolites, Hcy and MMA, knowingly neurotoxic [2,3,7,25] The Hcy increase can cause neurotoxicity through several mechanisms of which determine an acute imbalance between myelotoxic and trophic factors, with a subsequent increase of pro-inflammatory cytokines, toxins and free radicals and a decrease of growth factors synthesis [26]. So the prolonged use of LD and the HHcy may be responsible for axonal degeneration of sural nerve and by PN[7].

This study examined the possible association between dose, levodopa exposure duration, severity of Parkinson's disease, deficiency of VB12, folate, elevation of Hcy and MMA, and the development of neuropathy in IPD. However, our data were not conclusive, maybe because the small size of the sample and low prevalence of PN in participants (3/36 with IPD and 1/30 controls). No association were found between the aforementioned parameters and the neuropathy development. The serum levels of VB12 were normal in all the three affected (228 pg/mL min, 367pg/mL max). The HHcy was observed in all PN patients including the IPD carrier that did not use LD and control.

Our results do not corroborate the results obtained by Toth et al[2,3] who demonstrated association between prolonged use of LD, increase of the MMA and PN. This association had also been challenged by other researchers [13-15] who did not confirm the results obtained by Toth et al [2,3].

Data from this study suggests that the IDP by itself and the disease duration are the main factors that favored the development of neuropathy, since all patients with PN had five or more years of disease. The individual whit IPD and neuropathy has longer disease and treatment (12 years), showed greater motor impairment evidenced by the UPDRS III (66 points) and damage of daily living activities UPDRS II (37 points), suggesting that progression of the neurodegenerative process is an important risk factor for neuropathy. Our results are in agreement with those found by Chovancova et al and Shahrizaila et al., who found PN in individuals with advanced stages of the disease.

In our study, the MMA dosage was performed in urine and all results were negative. Is necessary to confirm this evidence by performing MMA dosage in blood in view of it is an exam with greater sensitivity and specificity for the diagnosis of VB12 deficiency.

We choose to perform a reduced NCS, because our aim was to study the PN and, in most of cases, the PN initially affects the lower limbs. Furthermore, was followed the simplified protocol adopted by the American Academy of Neurology [19].

In the NCS, the main change found was the decreased of CMAP amplitude in peroneal nerves. It was associated with decreased ankle tendon reflexes and vibratory sensitivity, but preservation of proprioception, even without objective change of surface sensitivity. This findings, confirmed the diagnosis of axonal neuropathy. A similar result was found by Okuma [10] in patients with ARJP.

Among the changes detected in the NCS, individuals with IPD showed changes in the peroneal and sural nerves that despite not meeting the criteria for PN diagnosis, may be an evidence of incipient PNS impairment and that the genetic predisposition may be a determinant factor for the development of neuropathy [4]. These changes may become more evident with disease progression, emphasizing the need for monitoring and revaluation of these patients.

It emerges from our study that the etiology of peripheral neuropathy in PD remains undefined. The possibility of being multifactorial, should be included indicating the need for further prospective studies with larger sample sizes to be able to defining the true role of exposure to LD, metabolic changes linked to VB12, of the genetic predisposition and the progression of the neurodegenerative process in the establishment of neuropathy.

ACKNOWLEDGEMENTS

We would like to thank the direction of the HUAC by release of laboratory tests; the doctor Alexandre Nóbrega Marinho for the statistical assistance and to Alysson G. Pascoal, Geneton R. de França and Felipe Henrique A. da Costa academics of Medicine course of the UFCG for their assistance in acquisition of data.

REFERENCES

1. Andrade LAF, Azevedo-Silva SM. Tratamento da Doença de Parkinson. In: Teive HAG, ed. Doença de Parkinson: um guia prático para pacientes e familiares. São Paulo: Lemos editorial: 2000;47-54.

2. Toth C, Brown MS, Furtado S, et al . Neuropathy as a potential complication of levodopa use in parkinson's disease. Mov Disord 2008;23:1850-1859.

3. Toth C, Brethaaupt K, Ge S, et al. Levodopa, methylmalonic acid, and neuropathy. In: idiopatic Parkinson. Ann Neurol 2010;68: 28-36.

4. .Rajabally, Yusuf A. Neuropathy in Parkinson disease: Prevalence and determinants. Neurology 2011;77(22):1947-1950.

5. Ceravolo R, Cossu G, di PoggioM.B et al .Neuropathy and levodopa in Parkinson's disease:Evidence from a multicenter study. Mov Disord 2013; 28:1391-1397.

6. Chovancova Z, Kanovsky P, DufeK J, et al. Peripheral nerve involvement and severity of motor disorder in Parkinson disease: a correlation study. Biomed Pap Med FacUnivPalacky Olomouc Czech Repub 2009;153(1): 59-62.

7. Müller T, Renger K, Kuhn W . Levodopa-associated increase of homocysteine levels and sural axonal neurodegeneration. Arch Neurol 2004;61:657-60.

8. Mancini F, Comi C, Oggioni G.D, et al. Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens. Parkinsonism and Relat Disorders 2014;20:27-31.

9. Shahrizaila N, Mahamad U.A, Yap A-C, Choo Y-M, Marras C and Lim S-H.Is chronic levodopa therapy associated with distal symmetric polyneuropathy in Parkinson's disease? Parkinsonism and Relat Disorders 2013;19:391-393.

10. Okuma Y, Hattor N, Yoshikuni M. Sensory neuropathy in autosomal recessive juvenile parkinsonism (PARK2). Parkinsonism and Relat Disorders 2003:313-314.

11. Manca D, Cossu G, Murgia D, et al. Reversible ecephalopathy and axonal neuroathy in Parkinson's disease during duodopa therapy. MovDisord 2009;24:2293-2294.

12. Urban PP, Wellach I, Faiss S, et al. Subacute axonal neuropathy in Parkinson disease with cobalamin and vitamin B6 deficiency under duodopa therapy. MovDisord 2010;25:1748-1752.

13. Montastruc JL, Lacroix I, Olivier P, et al (2010). Neuropathy as a potential complication of levodopa use in Parkinson disease: a pharmacological and pharmacovigilance point of view. MovDisord 2010;25:660-661.

14. Teodoro T, Pires D, Rosa MM, Coelho M, Sampaio c, Ferreira J .Has ”levodopa-induced neuropathy” been reported in Parkinson’s disease trials? MovDisord 2011;26:1966.

15. Nolano M, Provitare V, Lanzillo B and Santoro L. Neuropathy in Idiopatic Parkinson Disease: An iatrogenic Problem? Annals of Neurology (2011); vol.69:428-429.

16. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopatic Parkinson’s Disease: a clinicopathological study of 100 cases. J Neurol Neurosurg Psychiatry1992;51:181-184.

17. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology1967; 17:427-42.

18. Movement Disorders Society Task Force on Rating Scales for Parkinson’s Disease. The Unified Parkinson’s Disease rating scale (UPDRS): status and recommendations. Mov Disord 2003;18:738-750.

19. England JD, Gronsth GS, Franklin G, et al . Distal symetric polyneuropathy: a definition for clinical research. Neurology2005;64:199-207.

20. Bril V, Perkins BA. Validation f the Toronto clinical scoring system for diabetic polyneuropathy. Diabetes Care2002;25:2048-2052.

21. Moreira RO, Castro AP, Papelbaum M, et AL. Tradução para o português e avaliação da confiabilidade e uma escala para diagnóstico da polineuropatia distal diabética. Arq. Bras Endocrinol Metab2005;49(6):944-950.

22. Taly AB, Muthane UB. Involvement of peripheral nervous system in juvenile Parkinson’s disease. Acta Neurol Scand 1999;85:272-275.

23. Grandini DL, Nóbrega JAM, Juliano Y. Valores normais das velocidades de condução nervosa em um grupo de 101 pessoas. Arq Neuropsiquiatr 1992; 50(1): 50-55.

24. Nolano M, Provitare V, Estraneo A, et al . Sensory déficit in Parkinson disease: evidence of a cutaneous denervation. Brain 2008;131: 1903-1911.

25. Rogers JD, Sanchez-Saffon, Frol AB and Diaz-Arrastia R. Elevated plasma homocysteine levels in patients treated with levodopa. Arch Neurol 2003; 60: 59-64