DOI:10.4274/Tnd.58672

Original Article / Özgün Araştırma

Assessment of Early Stage Non-Motor Symptoms in Parkinson's Disease

Erken Evre Parkinson Hastalığında Motor Olmayan Semptomların Değerlendirilmesi

Haluk Gümüş[1], Zehra Akpınar[2], Orhan Demir[2]
[1]Konya Training and Research Hospital, Department of Neurology, Konya, Turkey
[2]Necmettin Erbakan University Meram Faculty of Medicine, Department of Neurology, Konya, Turkey

Summary

Objective: In this study, our purpose is to asses the frequency of non-motor symptoms and to discuss its effect on the morbidity of the disease.

Material and Method: We included 80 Parkinson's patients diagnosed according to the United Kingdom Brain Bank Criteria with a clinical stage of Hoehn Yahr stages 1 and 2, who were followed in the Department of Neurology.

Results: We have seen an increase in the frequency of non-motor symptoms in patients with higher UPDRS scores.

Discussion: Non-motor symptoms in Parkinson's disease can often go unnoticed. The success of the treatment also depend on the symptomatic treatment. Therefore, non-motor symptoms should be detected and treated early during the course of the disease. *(Turkish Journal of Neurology 2013; 19:97-103)*

Key Words: Parkinson's Disease, stage, non-motor symptoms

Özet

Amaç: Bu çalışmadaki amacımız erken evre Parkison Hastalığı'nda (PH) motor olmayan semptomların sıklığını araştırmak ve hastalığın morbiditesi üzerine etkisinin tartışılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya Selçuk Üniversitesi Meram Tıp Fakültesi Nöroloji polikliniğinde takip edilmekte olan United Kingdom Beyin Bankası Parkinson Hastalığı tanı kriterlerine göre Parkinson Hastalığı tanısı almış ve Hoehn Yahr klinik evrelemesine göre Evre 1 ve 2 olan 80 hasta alındı.

Bulgular: Olguların UPDRS skorları arttıkça motor olmayan semptomlarda belirgin düzeyde artma saptandı.

Sonuç: Parkinson hastalığındaki motor olmayan belirtiler sıklıkla gözden kaçıyor olabilir. Semptomatik tedavi önemli bir kısmında başarılıdır. Bu nedenle PH'da motor olmayan belirtilerin erken tanınması ve onların uygun olarak tedavi edilmesi çok önemlidir. *(Türk Nöroloji Dergisi 2013; 19:97-103)*

Anahtar Kelimeler: Parkinson hastalığı, evre, motor olmayan semptomlar

Introduction

Parkinson's Disease (PD) is a progressive movement disorder (1). First identified in 1817 by James Parkinson, this disease develops as a result of nigrostriatal dopaminergic neurons. The nigrostriatal dopaminergic neuron involvement is associated with the motor symptoms and the most common manifestations include resting tremor, bradykinesia, rigidity and loss of balance (postural instability) (2,3). Even though PD's motor symptoms are emphasized in the clinical profile, many patients with PD also have complaints described as non-motor (4). The non-motor symptoms (NMS) include fatigue, depression, anxiety, reduced cognitive capacity, sleep disorders, constipation, urinary bladder dysfunction, other autonomic disorders (sexual, gastrointestinal) and sensory disorders (5). These non-motor symptoms in PD are present not only in later stages but also in early ones and it was reported that first occurrence of symptoms such as loss of smell,

Address for Correspondence / Yazışma Adresi: Haluk Gümüş MD, Konya Training and Research Hospital, Department of Neurology, Konya, Turkey
Phone: +90 332 323 98 18 E-mail: dr.halukgumus@gmail.com
Received / Geliş Tarihi: 23.12.2012 **Accepted / Kabul Tarihi:** 07.05.2013

constipation, rapid eye movement (REM) sleep behavior disorder and depression can precede the motor symptoms of the disease by many years (ten years or more) (6). Recent studies documented how prolific these symptoms are and the severity of their impact on the patients' life quality, especially towards the later stages of the disease.

This study aims to investigate the frequency of NMS in early stage PD and to discuss their effect on the morbidity of the disease.

Materials and Methods

The study included 80 people from the pool of patients in Selçuk University Meram Faculty of Medicine who were diagnosed with PD according to United Kingdom PD brain bank diagnostic criteria and who were classified as Stage 1 and 2 in Hoehn Yahr clinical staging scale. Unified Parkinson's Disease Rating Scale (UPDRS) was used for the clinical rating. For the assessment of non-motor symptoms, non-motor scale (NMS scale) and non-motor questionnaire (NMS Quest) were used. Beck Depression Inventory (BDI) was used for depression diagnosis. Mini-Mental State Examination (MMSE) was used for the evaluation of cognitive functioning.

The acquired data was then analyzed with SPSS (Statistical package for the social sciences) 13.0 for Windows. The patients were compared in terms of their clinical and demographical properties using Mann-Whitney U test. A Chi-square test was used to investigate any possible differences between the study groups in terms of gender distribution and Hoehn-Yahr staging.

Results

The subject population included 60 male and 20 female patients with a mean age of 66.67±7.27. The mean age of the disease onset was 63.57±7.23 with the disease durations of 3.15±2.09 years. The mean for Hoehn Yahr clinical staging was 1.37±0.49 and the mean for UPDRS was 29.32±11.47. Twenty-three of the patients were not taking any medication, 33 were using L-Dopa, 13 were using a dopamine agonist, 11 were using MAO-B inhibitor and 3 patients were using two types of medication at the same time. The demographic properties of the sample are shown in Table 1.

The neuropsychiatric evaluation of the sample showed that 33 of the patients were suffering from depression. Twenty-one of these patients also had an anxiety disorder in addition to depression. Thirty of the depression cases were shown to be minor depression. Anxiety disorder was present in 26 patients and was being followed in the cases with depression diagnosis. Three of the patients also had findings suggesting apathy. None of the patients showed psychotic symptoms. After cognitive evaluation, 13 of the patients were seen to have attentional and concentration deficits with normal memory functioning. Sensory state evaluation showed that 44 patients had complaints of pain with 28 of them being neuropathic pain while 16 patients reported a cramp type, dystonic tensing pain. Autonomic dysfunction was seen in 38 patients with constipation and nocturia being the most commonly reported symptoms. Twenty four of the cases reported constipation, 22 reported frequent need to urinate, 15 reported orthostatic hypotension and 6 reported urinary retention. Ten patients showed increased sweating and oily skin. In terms of sexual functions, 12 patients reported erectile dysfunction and loss of libido and 3 showed hypersexuality. The cases where hypersexuality was seen were using dopamine agonist. In terms of sleep disorders, 52 patients reported insomnia and this was most commonly manifested as the inability to fall asleep. Seventeen of the patients reported REM sleep behavior disorder and 11 reported restless leg syndrome. None of the patients reported dysphagia or eating disorders. These findings are shown in Table 2. When Stage 1 and 2 cases were compared to each other, depression and anxiety disorder, cramp type pain and insomnia with difficulty falling asleep were seen more commonly in the Stage 2 patients. These findings are shown on Table 3. The same complaints seemed to worsen as the UPDRS score increased. The groups did not differ for other NMS.

Discussion

Despite the fact that the motor symptoms of PD has been defined extensively, the non-motor symptoms are still largely unknown and go untreated as a result. A recent study showed

Table 1. Demographic information of included cases

Number of cases	**80**
Sex	Male 60 (%75) Female 20 (%25)
Age	66,67±7,27
Age at disease onset	63,57±7,23
Disease duration	3,15±2,09
Hoehn-Yahr	1.37±0,49
UPDRS	29,32±11,47
L-Dopa use	33 (%41,25)
Dopamine agonist use	13 (%16,25)
MAO-B use	11(%13,75)
Use of dual medicine	3 (%3,75)

that 62% of the non-motor symptoms such as apathy, pain, sexual dysfunctions, bowel incontinence and sleep disorders were not reported to the health professionals due to patient's embarrassment or their lack of knowledge on the definition of the disease (7). This poses a problem for the patient by delaying the proper treatment and increasing the cost of care, also increasing the duration of hospitalization.

Measurement instruments with properly established validity do exist for the assessment of non-motor symptoms, including NMSQuest, NMS Scale and modified UPDRS, which we use in the our present study (8).

The non-motor symptoms in PD are present not only in later stages but also in early ones and that first occurrence of symptoms such as loss of smell, constipation, rapid eye movement (REM) sleep disorder and depression may precede the motor symptoms of the disease by many years (ten years or more) (6). A British study that included 433 patients reported that 91 of the patients (21%) sought medical help because of non-motor symptoms (9). There is a strong link between the presence of non-motor symptoms prior to motor PD diagnosis, and the progression of Lewy pathology in PD (10). It is known that Lewy body accumulation and neural dysfunction starts from the olfactory bulb and the lower parts of medulla, even though the motor symptoms of PD are not visible until dopaminergic neural loss in the pars compacta of substantia nigra. The primary dopaminergic regions, that is, pars compacta of substantia nigra, ventral tegmental area, and hypothalamus project over four main pathways: mesocortical, mesolimbic, nigrostriatal and tuberoinfundibular. These pathways play a role in the development of certain non-motor symptoms such as cognitive deficits, sleep and pain.

Table 2. Non-motor symptoms in the study group

Number of cases = 80	%
Neuropsychiatric disorders	38 (%37)
Depression	33
Depression + anxiety disorder	21
Anxiety	26
Apathy	3
Psychosis	-
Cognitive dysfunction	13 (%16)
Attention and concentration impairment	13
Memory impairment	-
Sensory symptoms	44 (%55)
Pain	44
Neuropathic pain	28
Cramp style pain (Dystonic tensing)	16
Autonomic dysfunction	38 (%37)
Constipation	24
Frequent urination	22
Orthostatic hypotension	15
Urinary retention	6
Excess sweating, oily skin	10
Sexual dysfunction	15 (%19)
Erectile dysfunction, loss of libido	12
Hypersexuality	3
Sleep disorders	58 (%73)
Insomnia	52
REM sleep behavior disorder	17
Restless leg syndrome	11
Gastrointestinal disorders	
Dysphagia	-
Eating disorders	-

The studies on neuropsychiatric symptoms reveal a large variety of non-motor symptoms including anxiety, depression or even dementia. Depression is an important neuropsychiatric symptom in PD and it can be observed in up to 45% of the cases (11). One study reported 40% incidence rate of depression whereas in another study the incidence rate of major depression is 2.7-70% (11). The depression in PD may be of mild severity and present with loss of self-confidence, anxiety and irritability while the feelings of guilt and failure are not as pronounced. The loss of dopaminergic, serotoninergic and noradrenergic innervation in the limbic system may be responsible for the dysfunction (12). In our study, we observed depression in 33 patients (41.25%). Twenty-one of these cases also showed anxiety disorders. Thirty of the 33 patients with depression diagnosis satisfied the criteria for minor depression. Anxiety disorder was mostly seen in patients with depression, together with motor fluctuations (13). In our study, 26 (32.5%) patients showed anxiety disorders and in 21 (87%) of them, it was together with depression. Apathy can be seen with depression or anxiety or can be present by itself. We observed symptoms for apathy in 3 (3.75) of our patients and they were seen in patients with major depression and anxiety disorder. We did not observe psychosis in any of our cases. Cognitive impairment is a symptom seen in 80% of the late-stage PD patients (14). But cognitive dysfunction may develop also in the early stages of PD and be manifested as adaptation and response difficulty or visual deficits (15). A study including 126 patients with early-stage PD diagnosis showed that 72 (57%) of the patients showed mild cognitive deficits (16). In our study, 13 out of 80 patients (16.3%) showed cognitive dysfunction. This dysfunction was in the form of attentional and concentration deficit and difficulty in decision making in all of 13 patients. None of the patients

Table 3. Evaluation of non-motor symptoms in Stage 1 and Stage 2 patients

Number of cases	Stage 1: 43 cases	Stage 2: 37 cases
Neuropsychiatric disorders	18 (%41.8)	20 (%54.0)
Depression	14 (%32.5)	19 (%51.4)
Depression + anxiety disorder	9 (%20.9)	12 (%32.4)
Anxiety	12 (%27.9)	14 (%37.8)
Apathy	1 (%2.3)	2 (%5.4)
Psychosis	-	-
Cognitive dysfunction	6(%14.0)	7 (%18.9)
Attention and concentration impairment	6 (%14.0)	7 (%18.9)
Memory impairment	-	-
Sensory symptoms	23 (%53.4)	21 (%56.7)
Pain	16 (%37.2)	12 (%32.4)
Neuropathic pain	7 (%16.3)	9 (%24.3)
Autonomic dysfunction	21 (%48.8)	17 (%45.9)
Constipation	13 (%30.2)	11 (%29.7)
Frequent urination	12 (%27.9)	10 (%27.0)
Orthostatic hypotension	8 (%18.6)	7 (%18.9)
Urinary retention	3 (%6.9)	3 (%8.2)
Excess sweating. oily skin	6 (%14.0)	4 (%10.8)
Sexual dysfunction	8 (%18.6)	7 (%18.9)
Erectile dysfunction. loss of libido	7 (%16.3)	5 (%13.5)
Hypersexuality	1 (%2.7)	2 (%4.7)
Sleep disorders	31 (%72.1)	27 (%73.0)
Insomnia	26 (%60.5)	26 (%70.3)
REM sleep behavior disorder	8 (%18.6)	9 (%24.3)
Restless leg syndrome	6 (%14.0)	5 (%13.5)
Gastrointestinal disorders	-	-
Dysphagia	-	-
Eating disorders	-	-

showed memory impairments and this was explained by the fact that only early stage cases were included.

Sleep disorders are among common non-motor symptoms in PD. Insomnia can be present as difficulty falling asleep or as disrupted sleep. Insomnia, especially disrupted sleep is particularly common among the patient population (>50%) (17). While sleep onset insomnia is primarily related to PD itself and its effects on the sleep, disrupted sleep is a non-motor symptom associated with nocturnal akinesia and off states (18). Restless leg syndrome in PD and the periodic extremity movements are closely related to dopamine and they constitute common causes for sleep disorders (19, 20). REM sleep behavior disorder is a type of parainsomnia characterized by vivid, extraordinarily scary nightmares. Paradoxal simple or complex movements seen in REM, where the muscles are generally atonic, accompany such nightmares (21). REM sleep behavior disorder may develop

prior to the disease itself. A study by Postuma and colleagues showed that 17.7% of the patients diagnosed with REM sleep disorder in the absence of parkinsonism were later diagnosed with a neurodegenerative disease within 5 years, and 40.6% of them in 10 years (22).

Fifty-eight (72.5) among the 80 people in our study reported sleep disorders. The most common one, sleep onset insomnia, was seen in 52 cases and patients expressed they cannot fall asleep. Sleep disruption was seen in only 5 of these 52 cases and they complained for frequently waking up during sleep. Seventeen (34.3%) of our cases satisfied the criteria for REM sleep behavior disorder and these complaints were mostly communicated by spouses or the caretakers of the patients. Eleven of our patients met the diagnostic criteria for restless leg and this was the common complaint with the patients with sleep onset insomnia.

The autonomic disorders in PD are also among common non-motor symptoms. Autonomic deficiency was seen in more than half of the Parkinson patients. One study reported the incidence rate of autonomic dysfunction as 47% (23). One of such dysfunctions is the urinary bladder dysfunction. The dopaminergic system has inhibitory and excitatory effects on the pontine micturition center (24). Bladder dysfunction may occur as a result of this interaction. Seventy-one percent of the patients show urinary system autonomic dysfunctions (25). Extreme detrusor activity, being commonly seen in PD, is associated with insufficient D1 activity or increased D2 activity and presents as urge urinary incontinence. Another urinary bladder dysfunction is the bladder contractibility disorder manifested as effortful urination (26). In NMS Quest study, 62% of the patients reported nocturia, which is a product of increased night-time urination, decreased bladder capacity and the sleep disorder due to nocturnal akinesia (28). There have been reports of hypersexuality or abnormal sexual behavior (dopamine dysregulation syndrome) especially due to dopaminergic medicine use (29). The oily skin cab be due to overactive sebaceous glands in the skin and redness, itchiness or flakiness can be due to seborrheic dermatitis. Increased sweatiness, can be due to disrupted control of sweat glands or the insufficiency of PD treatment. Constipation is a common non-motor function in PD and it is thought to be secondary to both central and colonal dopaminergic neuron losses (30). Twenty to thirty-six percent of the PD patients experience constipation (31). Orthostatic hypotension emerges frequently towards the later stages of PD and is symptomatic in 30-47% of the cases (31).

We detected autonomous dysfunction in 38 (37.25) of our patients. The most frequent autonomous dysfunction was constipation and it was seen in 24 of the cases. Twenty-two patients reported frequent need to urinate, 15 reported orthostatic hypotension, 10 reported oily skin and increased sweating and 6 reported urinary retention.

Sensory symptoms are seen in 40-50% of PD patients. Pain is the most frequent symptom. Dopamine is able to modulate the pain on several levels in the nervous system including spinal cord, thalamus, periaqueductal gray matter, basal ganglia and cingulate cortex (32). Non-Motor Symptoms Quest study reported pain in 29% of the patients (27). Another study found at least one type of chronic pain in 62% of the patients (33). The primary causes for pain in PD are the motor fluctuations secondary to the dopaminergic treatment and dyskinesia. Additionally, PD patients may show centralized pain, orofacial pain, extremity pain or musculoskeletal pain. They may present as cramp type, neuralgic or burning, hurting, coldness or throbbing (neuropathic pain) (34). In our study 44 patients (55%) had pain symptoms. Twenty-eight of these cases had neuropathic pain and 16 of them had cramp type dystonic pains.

Gastrointestinal system disorders are also seen in PD. Gastroparesis and difficulty in swallowing is seen in late-stage cases. These conditions were not present in our study since we only included early-stage cases.

Depression and anxiety were more common among Stage 2 cases compared to Stage 1. Both of the patients who were diagnosed with major depression were Stage 2. When the severity was measured using UPDRS in these cases, the depression and anxiety seemed to get higher as the severity increased. The conclusion drawn from this was that the stress induced by the progression of the disease is a contributing factor to depression and anxiety. The UPDRS score also increased as a function of cramp style pain in Stage 2 cases. Similarly the sleep onset insomnia was more frequently seen. This finding implies that the pain increases as the disease progresses, which makes it harder to fall asleep. It was an interesting finding that the groups did not differ in terms of other non-motor symptoms.

The debilitating non-motor symptoms of PD, which affect most of the patients, are the result of PD pathologies involving the nervous system outside of dopaminergic, nigrostriatal systems. Non-motor symptoms can easily be overlook in PD. Symptomatic treatment is often successful in a large portion of NMS. For this purpose, it is of crucial importance to recognize and treat NMS early on. The diagnoses of NMS in PD are based on clinical features. The first step is to inquire about the existence of these symptoms in the medical history. The reason for this is that the link between these symptoms and PD may not be immediately obvious to the patient and they may not readily grasp the necessity of reporting such symptoms. For this purpose, the symptoms should be brought up also during the subsequent follow-up visits.

References

1. Hilker R, Schweitzer K, Coburger S, Ghaemi M, Weisenbach S, Jacobs AH, Rudolf J, Herholz K, Heiss WD. Nonlinear progression of Parkinson disease as determined by serial positron emission tomographic imaging of striatal fluorodopa F 18 activity. Arch Neurol 2005;62(3):378-382.
2. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368-376.
3. Jankovic J, Shannon KM. Movement disorders. In: Bradley WG, Daroff RB, Fenichel GM, Jankovic J, editors. In: Neurology in Clinical Practice. Chapter 75. 5th ed. Philadelphia: Butterworth-Heinemann; 2008. p. 2081-2122.
4. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: Diagnosis and management. Lancet Neurol 2006;5:235-245.
5. Fahn S, Jankovic J. Principles and Practice of Movement Disorders, Churchill Livingstone/Elsevier, 2007.
6. Naidu Y, Chaudhuri KR. Early Parkinson's disease and non motor issues, J Neurol 2008;255:33-38.
7. Mitra T, Naidu Y, Martinez-Martin P, et al. The non declaration of non motor symptoms of Parkinson's disease to healthcare professionals. An international survey using the NMSQuest. 6th İnternational Congress on Mental Dysfunctions and other Non-motor Features in Parkinson's disease and Related Disorders. Dresden October, 2008. Park Related Disorders P011:161.
8. Chaudhuri KR, Martinez-Martin P. Quantitation of non-motor symptoms in Parkinson's disease. Eur J Neurol 2008;15:2-7.
9. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveria-Moriyama L, Lees AJ. Non motor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord 2008;23:101-106.
10. Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Stenur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-210.
11. Burn DJ. Beyond the iron mask;towards better recognition and treatment of depression associated with Parkinson's disease. Mov Disord 2002; 60:387-392.
12. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 2005;128:1314-1322.
13. Lemke MR, Brecht HM, Koester J, Kraus PH, Reichmann H. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. J Neuropsychiatry Clin Neurosci 2005;17:214-220.
14. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003;60:387-392.
15. Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. J Neurology 1997;244:2-8.
16. Williams-Gray C, Foltynie T, Brayne C, Robbins T, Barker R. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007;130:1787-1798.
17. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008; 79:368-376.
18. Dhawan V, Healy DG, Pal S, Chaudhuri KR. Sleep-related problems of Parkinson's disease. Age Ageing 2006;35:220-228.
19. Muzerengi S, Lewis H, Chaudhuri KR. Restless legs syndrome: a review of diagnosis and management. Int J Sleep Disord 2006;1:34-46.
20. Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. Arch Neurol 2002;59:421-424.
21. Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 2002;15;25:120-138.
22. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296-1300.
23. Seki S, Igawa Y, Kaidoh K, Ishizuka O, Nishizawa O, Andersson KE. Role of dopamine D1 and D2 receptors in the micturition reflex in conscious rats. Neurourology Urodyn 1992;11:535-545.
24. Allcock LM, Ullyart K, Kenny RA, Burn DJ. Frequency of orthostatic hypotension in a community based cohort of patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:1470-1471.
25. Uchiyama T, Sakakibara R, Hattori T, Yamanishi T. Short-term effect of a single levodopa dose on micturition disturbance in Parkinson's disease patients with the wearing-off phenomenon. Mov Disord 2003;18:573-578.
26. Zesiewicz TA, Baker MJ, Wahba M, Hauser RA. Autonomic Nervous System Dysfunction in Parkinson's Disease. Curr Treat Options Neurol 2003;5:149-160.
27. Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, MacPhee G, Brown RG, Naidu Y, Clayton L, Abe K, Tsuboi Y, MacMahon D, Barone P, Rabey M, Bonuccelli U, Forbes A, Breen K, Tluk S, Olanow CW, Thomas S, Rye D, Hand A, Williams AJ, Ondo W, Chaudhuri KR. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. Mov Disord 2007;22:1623-1629.
28. Bronner G, Royter V, Korczyn AD, Giladi N. Sexual dysfunction in Parkinson's disease. J Sex Marital Ther 2004;30:95-105.
29. Tolosa E, Katzenschlager R. Pharmacological management of Parkinson's disease. In: Jankovic J, Tolosa E, editors. Parkinson's Disease and Movement Disorders. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 110-145.

30. Singharam C, Ashraf W, Gaummitz EA, et al. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. Lancet 1995;346:861-864.
31. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain 1995;60:3-38.
32. Poewe W. Non-motor symptoms in Parkinson's disease. In: Jankovic J, Tolosa E, editors. Parkinson's Disease and Movement Disorders. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 67-76.
33. Nègre-Pagès L, Regragui W, Bouhassira D, Grandjean H, Rascol O; DoPaMiP Study Group. Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey. Mov Disord 2008;23:1361-1369.
34. Chaudhuri KR, Healy DG, Schapira AH.t National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5:235-245.