CLINICAL STUDIES / ETUDE CLINIQUES

COMPARISON OF CAUSES AND MANIFESTATIONS OF PAIN IN PARKINSON'S DISEASE PATIENTS TO HEALTHY CONTROLS

COMPARAISON ENTRE PATIENTS ATTEINTS DE LA MALADIE DE PARKINSON ET SUJETS SAINS, DES CAUSES ET DES MANIFESTATIONS DE LA DOULEUR

RANA Abdul Qayyum [1]
GALANGE Patrick [2]
KHAN Adeel [2]
SIDDIQUI Ishraq [3]

1. Parkinson's Clinic of Eastern Toronto and Movement Disorders Centre, Toronto, Ontario, Canada
2. University of Ottawa, Faculty of Medicine, Ottawa, Ontario, Canada
3. University of Toronto, Faculty of Neuroscience, Toronto, Ontario, Canada

E-Mail Contact - RANA Abdul Qayyum : ranaaq (at) yahoo (dot) com

Key words: *Healthy controls, movement disorders, pain, Parkinson's disease*

ABSTACT

Objective
To assess the manifestations of pain in PD (Parkinson's disease) patients versus healthy controls.

Methods
Data on pain was collected from 127 patients and an equivalent number of controls using two self-report questionnaires: the Brief Pain Inventory (BPI) and a custom-made questionnaire focusing on specific details not covered by the former. Additional analysis was conducted within the patient group only to analyze the potential effects of factors relating to PD on the various measure of interest relating to pain.

Results
Parkinson disease patients had lower odds of experiencing pain in both arms (ExpB=0.061, p<0.001), greater probability of demonstrating pain in both legs (ExpB=2.409, p=0.024), and an increase difficulty in localizing pain (ExpB=2.958, p=0.030). There was no relationship between duration of pain (F=12.414, p=0.001) or arthritis (ExpB=0.724, p=0.309) and pain in PD. The likelihood of experiencing nagging pain (ExpB=3.533, p=0.028), but not other forms, was much more strongly associated with PD patients than normal controls. When all other types of pain were controlled for, pain in PD is more likely associated with akathesic pain (ExpB=9.046, p<0.001).

Conclusion
There are major differences between pain in PD patients and pain in normal controls, which could have implications on the pathophysiology and adequate management of pain in different populations.

INTRODUCTION

Description and classification of pain in PD

While Parkinson's disease (PD) classically presents with tremor, rigidity, akinesia/bradykinesia and postural instability, patients often experience a much broader scope of symptomology [4, 27]. Later stages of this disease may manifest as dementia, depression, or psychosis [22]. Furthermore, over 90% of PD patients may experience non-motor symptoms, including pain [19]. Several studies, such as the case study by Djaldetti et al., have demonstrated that pain is much more frequent in patients with PD than in the healthy population [9]. Roughly 30-85% of patients with PD complain of experiencing pain, the large variation likely being accounted for by varying definitions and assessment tools [2]. Pain can be classified as either primary or secondary, the latter being more prevalent. Further classifications are achieved on the basis of major symptom etiologies [24].

Primary pain, or pain of central origin, is defined as pain that arises directly from the disease process itself [2, 24]. Patients may present with general discomfort or malaise. Alternatively, they may experience unexplained sensations in unexpected locations. These may be painful, stabbing, itching, burning, aching or tingling in character [24].

On the other hand, secondary pain arises from states that are consequent to PD [17]. The major etiologies of secondary pain include radicular/neuropathic pain, musculoskeletal (MSK) pain, akathisia, pain related to restless legs syndrome (RLS), and dystonia-related pain [24]. Radicular/neuropathic pain is due to a direct insult of the nervous system itself, and is characterized by persistent tingling, shooting, electrical or parasthetic sensation [1]. Pathology of the muscular and skeletal structures of patients with PD may lead to MSK pain. This is a potential consequence of rigidity and akinesia, which are both common early features of PD [16]. Akathisia is described as a psychological and physical irritability, where the patient is unable to remain still. It is a potential side effect of prolonged exposure to typical antipsychotic medications, such as Haloperidol, but may also be present in PD patients [24]. This is in contrast to RLS, where patients feel the urge to move but maintain voluntary control over their muscles. Furthermore, only RLS is tied to circadian rhythms [3]. Restless legs syndrome is diagnosed by the presence of the following four features: the urge to move limbs, accompanied by unpleasant sensations and feelings; worsened by rest and inactivity; relief through getting-up and moving around; and urges being the worst in the evening [3]. Of all the secondary causes of pain, dystonia is the most intense. Dystonia is a movement disorder characterized by painful twisting and unusual postures, which are secondary to sustained muscle contractions [15].

Management of pain in PD

Management of pain in PD may be achieved through either pharmacological or non-pharmacological approaches, or a combination of both [2]. The classification of pain as either primary or secondary helps to determine the ideal treatment regime. The sub-classification of secondary pain plays an additional role [24]. For example, the optimal treatment for MSK pain is a combination of MSK examinations; physical/occupational therapy; medical, anti-inflammatory, and dopaminergic therapies; and surgical alternatives, such as decompressive surgery when indicated [24]. On the other hand, pain related to akathisia is best managed with dopaminergic therapy, opioids and benzodiazepines [24]. Thus, safe and effective treatment strategies do exist. However, more focused research is needed to maximize effective pain management in PD patients [24].

Direction of our study

Pain affects individuals both physically and psychologically, ultimately impairing their ability to perform daily activities. Despite such a high prevalence, pain has yet to be well studied among PD patients. In our current study, we compare the prevalence of pain and its potential causes among PD patients to a similar group of control subjects. Among the individuals who experience pain, the reported severity, sensation, duration, and location are also analyzed.

MATERIALS AND METHODS

Study participants

Data was collected from 127 patients and an equivalent number of controls by a neurologist at a community-based Parkinson's disease and movement disorders center in 2013. Patients were diagnosed with idiopathic PD though UK Brain Bank Criteria, and were regularly assessed three to four times a year for follow-up care [14]. Patients ranged in age from 37 to 93 years. All patients were informed about the nature of the study and gave their written consent for participation. The local ethics review board approved of the study.

Study methods

Two self-report questionnaires were used: the Brief Pain Inventory (BPI) and a custom-made questionnaire focusing on specific details not covered by the former, including items specific to PD [6]. Participants were screened based on the presence of focal or generalized body pain, such as headaches. A negative finding would exclude the patient from our study. Participants provided information for potential causes by giving accounts of past medical history as well as other relevant events. Medical records were available to provide verification and additional details. The variables of interest relating to pain were compared within and between the groups to identify any differences in manifestation and/or cause. Patients were asked details on the nature of the pain experienced, such as onset, location, alleviating/exacerbating factors, quality, radiation, severity and timing. Additional sequelae, such as tingling, burning or cramping were assessed. Further analysis was conducted within the patient group to analyze the potential effects of factors relating to PD (side of body affected, Hoehn and Yahr stage, UPDRS score, etc.) on the various measure of interest relating to pain [13, 18]. Exclusion criteria included patients with atypical parkinsonism, drug-induced parkinsonism, as well as pain due to external causes and/or cognitive dysfunction.

Statistical methods

The causes and manifestations of pain in PD patients versus healthy controls were compared and assessed with Pearson correlations and multiple logistical regressions using SPSS version 19 (SPSS Inc., Chicago, IL, USA). A significance level of 0.05 was used throughout all of the analyses.

RESULTS

Pain in 127 patients with PD was compared to pain in an equivalent number of controls. Patients were assessed for the location of and ability to locate pain; the relationship between arthritis and duration of pain to pain in PD patients versus controls; the likelihood of experiencing various qualities of pain; as well as differences in the specific types of pain experienced.

Firstly, it was found that patients with PD had a decreased likelihood of experiencing pain in both arms when compared to controls (ExpB=0.061, P<0.001, Table 1). Furthermore, pain in either arm was not significantly correlated to the presence of PD in pain patients. Conversely, the odds of experiencing pain in both legs increased 2.4-fold in patients with PD (ExpB=2.409, P=0.024, Table 1). Interestingly, pain is almost three-times as difficult to locate in patients with PD when compared to normal controls (ExpB=2.958, P=0.030, Table 1). Further analysis demonstrated that there was not a significantly increased propensity of experiencing pain in PD for patients with arthritis (ExpB=0.724, P=0.309, Table 2) or a longer duration of pain (F=12.414, P=0.001, Table 3).

When assessed for likelihood of experiencing certain qualities of pain in PD patients versus healthy controls, only nagging pain was reported as being significantly more likely. Indeed, there was a 3.5-times greater probability of experiencing nagging pain in subjects with the onset of PD as opposed to those without (ExpB=3.533, P=0.028, Table 4). There was no difference in likelihood for aching, dull, tension, sharp, penetrating, shooting, throbbing, gnawing and numb pain. Radiating, boring, burning, stabbing and tender pain were excluded due to low sample size. When subjects were assessed for the likelihood of experiencing various types of pain in PD versus non-PD, patients with PD were found to be 9-times more likely to experience akathesic pain when other types of pain were held constant (ExpB=9.046, P<0.001, Table 5). Other forms of pain include non-localized, dystonic, and neuropathic pain. When akathesic pain was not controlled for, neuropathic pain became significant in PD patients (ExpB=2.530, P=0.018, Table 5). Further analysis found that patients with pain and PD had an increased chance of experiencing an interaction between akathesic and neuropathic pain (ExpB=3.862, P=0.027, Table 5). A summary of the PD+ and PD- populations that experienced certain locations, qualities, and types of pain is highlighted on Table 6.

DISCUSSION

Location of pain

Pain in PD is well recognized. Three recent reviews highlight the wide range of pain symptoms associated with PD and describe new ways of characterizing and classifying nociceptive, neuropathic and musculoskeletal pain of Parkinson's disease [10, 12, 29]. Our study found that PD patients are more likely to experience pain in both legs as compared to arms. Limb pain in the form of unilateral or bilateral shoulder

pain, hand and leg pain has previously been described in relation to PD and a recent review summarizes these and other locations of pain [10, 26]. Another recent study describes persistent leg pain as a distinct entity and provides information specific to this presentation [28]. This may help explain why PD patients are more likely to experience leg pain than arm pain.

Localization of pain

PD patients experiencing pain had greater difficulty identifying the precise location of pain when compared to healthy individuals. This may represent a novel finding, as to our knowledge, there is no literature comparing PD patients ability to localize pain to healthy individuals. We also found that PD patients were more likely to report their pain as aching when compared to healthy individuals. This is in agreement with another recent study, which found that the most common physical experience of pain in PD patients was aching [21].

Quality of pain

Our study demonstrates that patients with PD are 9-times more likely to experience akathesic pain when compared to healthy controls. It has already been established that Parkinson's disease is closely associated with akathisia, as both seem to arise from the basal ganglia [25, 30]. Indeed, akathisia has been found to occur in up to 45% of PD patients, and correlates with both the age of onset and severity of PD [7]. However, the basis of this association remains controversial, and has been postulated as a consequence of dopamine receptor blocking drugs, and not PD itself [21]. Another theory is that alterations in the mesocortical pathway, which is associated with the cognitive defects of PD, may be involved in the pathophysiology of akathisia [20]. Although a clear etiology has yet to be defined, our study adds further support to the increased prevalence of akathesic pain in patients with PD, and may provide insight for how patients can better manage their pain.

MSK comorbidities and pain in PD

The fact that patients with PD and arthritis were not more likely to experience pain than those with PD alone removes arthritis as a comorbidity that may compound our findings. Musculoskeletal problems are very common in PD as well as with the general population, and an important contributor to a decreased quality of life [31]. However, studies on the prevalence of arthritis and PD are conflicting, with some showing an increased prevalence, and others not [8, 23]. If there is in fact a greater prevalence of MSK problems in PD patients, the management of these symptoms should not be neglected, especially in post-deep brain stimulation (DBS) patients where it is a common complaint [11]. In addition, past studies have shown a positive correlation between MSK problems and pain in PD patients [31, 32]. Despite this possible association, pain in PD patients within our study population seems to have not been affected by arthritis. One possible explanation is that the MSK pain was overpowered by a concomitant akathesic pain. Regardless of the reason, more studies should be performed to clarify this discrepancy, and to elucidate a more definitive relation between arthritis and pain in PD.

Strengths and weaknesses of study

Compared to studies reported in the literature, the present study had a relatively large sample size and adopted a novel approach to the study of pain in the PD population. This approach, in addition to the standardized assessment methods used which may limit biases, is a significant strength of this study and was shown to be applicable to the study of PD-associated pain. Importantly, research with questionnaires filled out by PD patients and their caregivers may more accurately reflect feelings of pain in the life of PD patients. Excluding patients with cognitive dysfunction and dementia also helped to ensure the validity of patient accounts throughout the interview process. Another strength was that our analysis accounted for the effect of various localizations and types of pain. Our study is not without limitations, however. Neurophysiologic examinations may have been useful to objectify the classification into pain types in some cases (e.g. better define what is meant by "aching pain"). Secondly, the subjective nature of pain leaves some limitations to all studies of pain in humans. Finally, our group of healthy individuals was not aged-matched controls, thereby possibly limiting the strength of our results.

CONCLUSIONS

In spite of pain being a common NMS in PD, it continues to be under-reported and under treated as demonstrated in a recent study across European centres [5]. It is thought that these symptoms may remain undeclared to health-care professionals due to a lack of awareness by the patient that the symptoms are linked to PD. This highlights the need for enhanced awareness and a better understanding of pain in PD by clinicians. We therefore feel that the publication of more detailed information regarding pain phenotypes in PD is important, as this will promote early recognition and management of PD related pain. Our long-term goal would be to increase the chance of effective management, enabling a better quality of life for patients affected by this debilitating disease.

Conflit d'intérêt : Aucun

Table 1. Location of and ability to pinpoint pain in Parkinson's disease patients versus healthy controls.

Variable	N	B	SE	Wald	Significance	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Both Arms	17	-2.797	0.680	16.930	0.000	0.061	0.016	0.231
Constant	.	2.797	0.461	36.875	0.000	16.400	.	.
Both Legs	42	0.879	0.388	5.124	0.024	2.409	1.125	5.156
Constant	.	-0.032	0.178	0.032	0.859	0.969	.	.
Difficulty Locating Pain	24	1.084	0.501	4.693	0.030	2.958	1.109	7.890
Constant	.	0.014	0.168	0.007	0.933	1.014	.	.

Table 2. The relationship between arthritis and pain in Parkinson's disease patients.

Variable	*N*	*B*	*SE*	*Wald*	*Significance*	*Exp(B)*
Arthritis	40	-0.323	0.317	1.036	0.309	0.724
Constant	.	0.294	0.206	2.027	0.155	1.341

Table 3. The relationship between duration of pain (hours) and pain in Parkinson's disease patients.

	Levene's Test for Equality of Variances		t-test for Equality of Means				
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
Duration (hours)	12.414	0.001	1.916	106.000	0.058	17.140	8.944
	.	.	1.783	50.474	0.081	17.140	9.615

Table 4. Likelihood of experiencing various qualities of pain in Parkinson's disease patients versus normal controls. Radiating, boring, burning, stabbing and tender pain were excluded due to lack of sample size.

Sensations of Pain	N	B	SE	Wald	Significance	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Aching	90	0.419	0.474	0.783	0.376	0.658	0.260	1.664
Dull	44	-0.511	0.596	0.735	0.391	0.600	0.186	1.930
Tension	31	0.561	0.628	0.799	0.371	1.753	0.512	6.005
Sharp	42	0.780	0.534	2.137	0.144	2.182	0.766	6.214
Penetrating	24	0.155	0.573	0.074	0.786	1.168	0.380	3.588
Shooting	18	0.327	0.674	0.234	0.628	1.386	0.370	5.199
Throbbing	13	0.687	0.585	1.380	0.240	1.988	0.632	6.259
Gnawing	17	-0.748	0.683	1.197	0.274	0.473	0.124	1.807
Nagging	34	1.262	0.576	4.799	0.028	3.533	1.142	10.928
Numb	20	0.307	0.659	0.217	0.641	1.359	0.374	4.940
Constant	.	-0.043	0.520	0.007	0.934	0.958	.	.

Table 5. Likelihood of experiencing various types of pain in Parkinson's disease patients versus healthy controls. Pain type likelihood is assessed when all forms of pain are held constant and when all types minus akathesic pain are controlled for. Interactions between akathesic and neuropathic pain are also analyzed.

Analysis	Types of Pain	N	B	SE	Wald	Significance	Exp(B)	95% CI for Exp(B)	
								Lower	Upper
All pain controlled for	non-localized pain	17	-1.033	0.651	2.515	0.113	0.356	0.099	1.276
	Dystonic pain	67	0.283	0.375	0.570	0.450	1.327	0.636	2.768
	Neuropathic pain	52	0.588	0.422	1.940	0.164	1.800	0.787	4.114
	Akathesic pain	44	2.202	0.535	16.934	**0.000**	**9.046**	3.169	25.825
	Constant	.	-0.412	0.228	3.269	0.071	0.662	.	.
All pain but akathesic controlled for	non-localized pain	17	-0.614	0.550	1.246	0.264	0.541	0.184	1.591
	Dystonic pain	67	0.393	0.352	1.247	0.264	1.482	0.743	2.955
	Neuropathic pain	52	0.928	0.391	5.643	**0.018**	**2.530**	1.176	5.441
	Constant	.	-0.147	0.210	0.493	0.482	0.863	.	.
Interactions	Akathesic + neuropathic	96	1.359	0.583	5.433	**0.020**	**3.892**	1.241	12.202
	Constant	.	0.027	0.166	0.027	0.869	1.028	.	.

Table 6. Summary of the population that experienced pain with (PD+1) and without (PD+0) Parkinson's disease.

Location or characteristics of pain		PD+	
		0	1
		N	N
Right arm only	0	74	80
	1	2	10
Left arm only	0	70	79
	1	6	11
Both arms	0	5	82
	1	8	8
Right leg only	0	72	84
	1	4	6
Left leg only	0	70	78
	1	6	12
Both legs	0	64	62
	1	12	28
Aching	0	9	15
	1	31	49
Throbbing	0	34	44
	1	6	20
Shooting	0	34	44
	1	6	20
Stabbing	0	37	49
	1	3	15
Gnawing	0	33	54
	1	7	10
Sharp	0	31	40
	1	9	24
Tender	0	37	47
	1	3	17
Burning	0	34	45
	1	6	18
Exhausting	0	30	25
	1	10	39
Tiring	0	24	20
	1	16	44
Penetrating	0	36	46
	1	4	18
Nagging	0	32	39
	1	8	25
Numb	0	35	49
	1	5	15
Generalized body pain	0	67	82

	1	9	8
Cramping pain	0	53	52
	1	23	38
Neuropathic pain	0	63	58
	1	13	32
Akathsic pain	0	71	54
	1	5	36

REFERENCES

1. BEISKE AG, LOGE JH, RONNINGEN A, SVENSSON E. Pain in Parkinson's disease: prevalence and characteristics. Intern Assoc for the Study of Pain. 2009;141:173-77.
1. BERARDELLI A, CONTE A, FABBRINI G, BOLOGNA M, LATORRE A, ROCCHI L, SUPPA A. Pathophysiology of pain and fatigue in Parkinson's disease. Parkinsonism and Related Disorders. 2012;18S1:S226-S228.
2. BOGAN RK, CHERAY JA. Restless legs syndrome: a review of diagnosis and management in primary care. Postgrad Med. 2013;125:99-111.
3. BRAAK H, DEL TREDICI K, RUEB U, DE VOS RA, JANSEN STEUR ENH, BRAAK E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24:197-211.
4. CHAUDHURI KR, PRIETO-JURCYNSKA C, NAIDU Y, MITRA T, FRADES-PAYO B, TLUK S, RUESSMANN A, ODIN P, MACPHEE G, STOCCHI F, ONDO W, SETHI K, SCHAPIRA AH, MARTINEZ CASTRILLO JC, MARTINEZ-MARTIN P. The non declaration of non motor symptoms of PD disease to health care professionals: an international study using the non motor symptoms questionnaire. Mov Disord. 2010;25:704-709.
5. CLEELAND CS, RYAN KM. Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23:129-138.
6. COMELLA CL, GOETZ CG. Akathisia in Parkinson's disease. Mov Disord. 1994;9:545-549.
7. DEGAZIO G, BERARDELLI A, FABBRININ G, MARTINO D, FINCATIU E, FIASCHI A, MORETTO G, et al. Pain as a nonmotor symptom of Parkinson disease: evidence from a case-control study. Arch Neurol. 2008;9:1191-1194.
8. DJALDETTI R, SHIFRIN A, ROGOWSKI Z, SPRECHER E, MELAMED E, YARNITSKY D. Quantitative measurement of pain sensation in patients with Parkinson disease. Neurology. 2004;62:2171-75.
9. FIL AR, CANO-DE-LA-CUERDA E, MUNOZ-HELLIN L, VELA M, RAMIRO-GONZALEZ, FERNANDEZ-DE-LAS-PENAS C. Pain in Parkinson disease: a review of the literature Parkinsonism. Relat Disord. 2013;19:285-294.
10. GENTY S, DERREY S, POUPLIN S, LEFAUCHEUR R, CHASTAN N, GERARDIN E, MALTETE D. Pain due to osteoarthritis may impair the early outcome of deep brain stimulation in Parkinson's disease. Clin Neurol Neurosurg. 2011;10:864-867.
11. HA AD, JANKOVIC J. Pain in Parkinson's disease. Mov Disord. 2012;27:485-491.
12. HOEHN MM, YAHR MD. Parkinsonism: Onset, progression, and mortality. Neurology. 1967;17:427-442.
13. HUGHES AJ, DANIEL SE, KILFORD L, LEES AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinic-pathological study of 100 cases. JNNP. 1992;55:181-184.
14. KAWARAI T, MIYAMOTO R, MURAKAMI N, MIYAZAKI Y. Dystonia genes and elucidation of their roles in dystonia pathogenesis. Rinsho Shinkeigaku. 2013;53:419-29.
15. KIM YE, LEE WW, YUN JY, YANG HJ, KIM HJ, JOEN BS. Musculoskeletal problems in Parkinson's disease: Neglected issues. Parkinsonism Relat Disord. 2013;7:666-669.
16. LEE MA, WALKER RW, HILDRETH TJ, PRENTICE WM. A Survey of Pain in Idiopathic Parkinson's Disease. J Pain Symptom Manage. 2006;32:462-649.
17. MOVEMENT DISORDER SOCIETY TASK FORCE ON RATING SCALE FOR PARKINSON'S DISEASE. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Movement Disorders. 2003;18:738-750.
18. PARKINSON J. An essay on the shaking palsy. Sherwood, Neely and Jones, London, 1817.
19. PORTIN R, RINNE UK. Predictive factors for cognitive deterioration and dementia in Parkinson's disease. Adv Neurol. 1986;45:413-416.
20. RANA AQ, SAEED U, MASROOR MS, YOUSUF MS, SIDDIQUI I. A cross-sectioanl study investigating clinical predictors and physical experiences of pain in Parkinson's disease. Functional Neurology. 2013;28:297-304.
21. RIDENOUR TA, DEAN RS. Parkinson's disease and neuropsychological assessment. Int J Neurosci. 1999;99:1-18.
22. RUGBJERG K, FRIIS S, JORGENSEN TL, RITZ B, KORBO L, OLSEN JH. Risk for Parkinson's disease among patients with osteoarthritis: a Danish cohort study. Mov Dis Off J Mov Disord Soc. 2010;14:2355-2360.
23. SORBO FD, ALBANESE A. Clinical management of pain and fatigue in Parkinson's disease. Parkinsonism and Related Disorders. 2012;18S1:S233-S236.
24. STACY M. Nonmotor symptoms ion Parkinson's Disease. International Journal of Neuroscience. 2011;121:9-17.
25. STAMEY W, DAVIDSON A, JANKOVIC J. Shoulder pain: a presenting symptom of Parkinson's disease. J Clin Rheumatol. 2008;14:253-254.
26. VAN DEN BERGE SA, KEVENAAR JT, SLUIJS JA, HOL EM. Dementia in Parkinson's disease correlates with alpha-synuclein pathology but not with cortical astrogliosis. Park Dis. 2012:1-13.

27. WALLACE, CHAUDHURI. Unexplained lower limb pain in Parkinson's disease: A phenotypic variant of painful Parkinson's disease. 2014;20:122-124.
28. WASNER G, DEUSCHL G. Pains in Parkinson disease - many syndromes under one umbrella. Nat Rev Neurol. 2012;8:284-294.
29. WITJAS T, KAPHAN E, AZULAY JP, BLIN O, CECCALDI M, POUGET J, PONCET M, CHERIF AA. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology. 2002;3:408-413.
30. YOUNG EK, BEOM SJ. Musculoskeletal problems in Parkinson's disease. J Neuroal Transm. 2013;120:537-542.
31. YOUNG EK, WOONG-WII L, JI YY, HUI JY, HAN-JOON K, BEOM SJ. Musculoskeletal problems in Parkinson's disease: neglected issues. Parkinsonism and Related Disorders. 2013;19:666-669.