

PAIN IN PARKINSON'S DISEASE

Grace Helena Letro¹, Elizabeth M.A.B. Quagliato², Maura Aparecida Viana²

Abstract – Pain may precede the diagnosis in Parkinson's disease (PD). The goal of this study was to assess the pain in a group of 20 females and 30 males with PD, after excluding co-morbidities as causes. It was used the following tools: Unified Parkinson's Disease Rating Scale, McGill questionnaire and Beck Depression Inventory. In 27 patients (54%), the pain was associated with PD, occurring in 22 (44%) in the off period and 5 (10%) in both on and off periods. The off period resulted in an increased frequency of pain, which was related to stiffness. There was no association between pain and tremor in off period, neither between pain and Modified Hoehn and Yahr stage, nor the Schwab and England scale. It was not observed an association between pain and depression, neither between pain and dyskinesia. It was noticed the improvement in pain in 16 patients with levodopa (59.26%).

KEY WORDS: Parkinson's disease, pain, levodopa.

Dor na doença de Parkinson

Resumo – Dor pode preceder o diagnóstico na doença de Parkinson (DP). O objetivo deste estudo foi avaliar a dor num grupo de 20 mulheres e 30 homens com DP. Após a exclusão das co-morbidades como causa. Foi usado o seguinte: *Unified Parkinson's Disease Rating Scale*, o questionário de dor McGill e o Inventário de Depressão de Beck. Em 27 pacientes (54%), a dor associou-se com a DP, ocorrendo em 22 (44%) no período *off* e em 5 (10%) nos períodos *on* e *off*. O período *off* resultou num aumento da frequência da dor, o qual se relacionou com a rigidez. Não houve associação entre dor e tremor no período *off*, estágio *Hoehn e Yahr* modificado, nem a escala de *Schwab e England*. Não foi observado associação entre dor e depressão, nem entre dor e discinesia. Foi observada a melhora da dor em 16 pacientes com levodopa (59.26%).

PALAVRAS-CHAVE: doença de Parkinson, dor, levodopa.

Pain has been reported since the first descriptions of Parkinson's disease¹ (PD). It has been shown as an onset symptom of the disease occurring before motor symptoms. Patients with PD reported sensitive symptoms, preceding or following the motor picture (from 40% to 75%)^{2,3}. The causes of pain in PD are the co-morbidities, disease symptoms and complications of PD treatment itself. After the first months or years of levodopa treatment, motor and non motor fluctuations generally occur, triggered by the pharmacokinetic properties on this drug, leading to decreased effectiveness. Among the non motor symptoms it could be found sensitive, psychical, cognitive and autonomic changes. Pain fluctuates with motor symptoms^{6,7}, specially in the presence of stiffness and akinesia, but not related to tremor⁸. Stiffness and akinesia contribute to 1/3 of pain in PD cases⁸. Aching, cramping and joint pains frequently result from a lack of mobility in affected limbs³. Shoulder pain is a common complaint in PD, which may

precede the motor symptoms or may manifest itself during disease evolution. One of the two main types of shoulder pain in PD is the pseudorheumatic, directly related to neurological symptoms, which is dopamine responsive. The other one is pain due to degenerative lesions that could appear or worsen with PD. Another etiology of pain is the primary sensitive syndrome, frequent in young PD patients, whose cause is unknown, suggesting that the basal ganglia may contribute to nociception⁹. This pain is described as vague, poorly located, discomfort, tension, tickling, burning and it could precede the motor symptoms of PD, with little response to dopaminergic therapy^{2,9}. Genital pain usually occurs in perimenopausal or postmenopausal patients. In PD female patients, it may fluctuate with motor symptoms. Levodopa improves the pain in some cases, although in others it may worsen^{10,11}. Oral pain or burning mouth syndrome occurs more frequently in postmenopausal patients and it was reported in PD¹².

¹Post Graduation Student from the Neurology Department of Faculty of Medical Science from the University of Campinas, Campinas SP, Brazil; ²Clinic of Movement Disorders from the State University Hospital of Campinas (Unicamp), Campinas SP, Brazil.

Received 9 December 2008, received in final form 2 April 2009. Accepted 3 June 2009.

Dra. Grace Helena Letro – Rua Engenheiro Cândido Gomide 468 - 13070-200 Campinas SP - Brasil. E-mail: gletro@terra.com.br

Dyskinesias related to levodopa cycle may cause pain. Dystonia preferably occurs in the off period and generally on feet¹³. Primary parkinsonian pain is complex and may involve sensory pathways within the basal ganglia and the thalamocortical basal ganglia circuits¹⁴. Lesions in dorsal horn layer I, parasympathetic and sympathetic pre and postganglionic neurons were described in PD patients that were positive for α – synuclein¹⁵.

Goetz et al.⁴ used McGill questionnaire to evaluate pain in PD. This questionnaire is worldwide applied for other painful syndromes and it is also used in Brazil¹⁹.

The objective of this study to evaluate the frequency of pain in a group of 50 patients and correlate it to the worsen parkinsonian symptoms (off period), depression, dyskinesia and also to observe the levodopa effect in pain associated with PD.

METHOD

This prospective study was carried out from March 2005 to February 2006 in the Movement Disorders Clinic from the Neurology Department on the Clinical Hospital of the State University of Campinas. The 50 PD patients were included in this research after reading and signing the Free and Informed Consent approved by the Research Ethical Committee of the Faculty of Medical Sciences from the State University of Campinas.

Patients aged 40 years or more, with idiopathic PD according to the London Brain Bank criteria¹⁶ and taking levodopa were included in this study. A brain computer tomography (CT) or brain magnetic resonance imaging (MRI) was performed to exclude other diagnosis. Exclusion criteria were the use of dopamine blocker substances and a score of less than 20 on Mini Mental State Examination¹⁷ (MMSE). Patients remained without medication for 12 hours before the first assessment, being evaluated in off period. They were submitted to a questionnaire which included epidemiological data, sensitive and motor symptoms. The differential diagnosis between secondary pain to PD and osteoarthritis was established by both clinical history and physical examination. The patients were assessed with Unified Parkinson's Disease Rating Scale subscales II (daily activity), III (motor examination), IV (motor complications)¹⁸, V (modified Hoehn and Yahr staging) and VI (Schwab and England) in the off period. After these assessments, they took their usual doses of levodopa and were evaluated again after 60 minutes (on period), with both McGill questionnaire¹⁹ and Beck Depression Inventory (BDI)²⁰.

Spearman correlation was applied to study the relationship among the UPDRS subscales, the duration of disease time and pain total index. Methodological analysis of variance with rank transformation was applied to compare the pain total index to gender, depression and dyskinesia. In order to Fisher Test was used to assess the effects of levodopa in the pain.

Table 1. Demographic and clinical data of 50 PD patients.

Gender	Male 30 (60%) Female 20 (40%)
Mean age at onset of symptoms	54.84±9.54 Years
Mean duration of disease	8.06±4.77 Years
Symptoms	Stiffness / bradykinesia 4 (8%) Tremor / stiffness / bradykinesia 45 (90%) Tremor / stiffness / bradykinesia / postural instability 1 (2%)
Modified Hoehn and Yahr stage	Stage 1 4 (8%) Stage 1.5 2 (4%) Stage 2 23(46%) Stage 2.5 13 (26%) Stage 3 4(8%) Stage 4 4(8%)
Patients on levodopa therapy	50
Patients on dopamine agonist therapy	Zero
Depression	No depression 28 (56%) Mild to moderate depression 17 (34%) Moderate to severe 2 (4%) Major depression 3 (6%)
Dyskinesia	9 (18%) • Early morning dystonia – 2 patients • Painful dyskinesia – 1 patient • No disabling dyskinesia – 9 patients
No dyskinesia	41 (82%)

RESULTS

Table 1 shows demographic and clinical data of 50 PD patients.

Nine (18%) patients had one or more pains related to co-morbidities and some of them had also presented pain related to PD. Osteoarthritis was found in six patients (12%), radiculopathy L₄-L₅ in four (8%); disc hernia C₄-C₅ in two (4%) and disc hernia T₉-T₁₀ in one (2%). Patients with osteoarthritis presented pain through joint movements, improved with rest, analgesic and anti-inflammatory drugs.

In PD patients the pain appeared or increased during the periods of less mobility (off periods), when analgesics, antidepressants and anti-inflammatories drugs were ineffective.

This study observed that pain for PD appeared during evolution of disease, on the body side which presented more motor symptoms. Neuroimage examinations did not show changes on cervical, thoracic and lumbar spine CT or MRI. Table 2 shows evaluation of pain.

There was association between stiffness and pain in off period ($p=0.0315$), but not between tremor and pain ($p=0.7912$). There was a correlation between the activities of daily living (UPDRS subscale II) and pain during off period ($p=0.0146$), but it was not significant between motor

examination (UPDRS subscale III) and pain ($p=0.0563$). It was not observed association between modified Hoehn and Yahr staging ($p=0.09791$) and pain, neither the Schwab and England scale and pain in off period ($p=0.1602$), nor duration disease ($p=0.0523$) and pain (p value based on the correlation coefficient of Spearman).

Table 3 shows correlation among gender, depression and dyskinesia with pain.

DISCUSSION

In this study, it was observed that 54% of patients had pain, according to literature^{2,4,21,22}. The onset of pain occurred during the evolution of PD, on the body side which presented more motor symptoms. Predominance of pain was found in the off period in 44% of patients. Stiffness was suggested as a pain factor, but it was not occurred in relation to tremor. Studies have shown a predominance of pain in the off period and may be related to increase of stiffness^{3,4,23}. The onset of pain on the most affected body side does not mean that pain is caused only by stiffness and/or bradykinesia, a hypothesis that could show that both the pain and motor symptoms share similar mechanisms, what means that modulation of pain could be performed by dopaminergic pathways on basal ganglia, where the lack of dopamine leads to a painful condition^{10,24,25}.

Association between dyskinesia and pain was not seen as in others studies^{4,23}. Probably this is not observed, because the sample of dyskinesia patients was little and the methodology applied is for great sample.

Depression was not an important factor to trigger the pain. Starkstein et al. have shown that pain is significantly more severe in patients with major depression than in patients with minor or no depression²⁶. According to BDI, this study observed no depression in 56% of the patients, mild to moderate in 34%, moderate to severe in 4% and mayor depression in 6%. These data corroborated to Starkstein et al.²⁶, who concluded that the pain is more severe in patients suffering with major depression.

It was shown an association between activities of daily living (UPDRS-subscale II) in the off period, but it was not observed association between Schwab and England scale

Table 2. Evaluation of pain.

Pain	27 (54%)
No pain	23 (46%)
Pain attributed to osteoarthritis*	6 (12%)
Site of pain attributed to PD	limb 8 (16%) shoulder 7 (14%) generalized 5 (10%) lumbar 4 (8%) cervical 2 (4%) back 1 (2%)
Pain improvement under levodopa effect	16 (59.26%)
No pain improvement levodopa effect	11 (40.74%)

*These patients had also presented pain related to PD.

Table 3. Correlation among gender, depression and dyskinesia to pain.

Variables	n	Pain					p-value*
		Mean	SD	Min	Median	Max	
Male	30	11.03	13.98	0.00	3.00	46.00	0.3303
Female	20	15.05	16.60	0.00	9.50	53.00	
Depression	22	17.50	17.52	0.00	12.50	53.00	0.0733
No depression	28	8.82	11.75	0.00	0.00	37.00	
Dyskinesia	9	13.44	12.06	0.00	14.00	33.00	
No dyskinesia	41	12.46	15.75	0.00	7.00	53.00	0.5935

*p-value based on ANOVA with processing rank; n: sample; mean: average score of pain; SD: standard deviation; min: minimum; max: maximum.

ADL and pain in the off period. Although, this scale of activities of daily living is used to assess the severity of the disease, it was observed that UPDRS – subscale II was more sensible. Association between modified Hoehn and Yahr stage and pain was not observed. There has been a greater predominance of stage 2 (46%) and 2.5 (23%). Perhaps, this association had not occurred due to these stages which are minimally disabling²⁷ or because these patients on these stages are taking levodopa and responding this medication.

The improvement of the pain was found in 59.26% of the patients under levodopa effect. However, in 40.7% of these patients this was not observed, suggesting that in addition to the patients who were in “wearing-off” status, there must have been nondopaminergic mechanisms related to primary pain in PD¹⁴. Recent studies had shown a reduction of the threshold to pain in PD^{14,28}. Brefel-Courbon et al.²⁸ investigated the pain in PD patients and controls by means of thermal stimulation and cerebral activity with positron emission tomography. They concluded that pain threshold in PD patients in off condition was significantly lower than in controls and the administration of levodopa significantly raised pain threshold in PD patients, but not in controls. Moreover, PD patients have higher pain induced by activation in nociceptive pathways, which can be reduced by levodopa.

Gender and duration of disease were equivalent between the two groups (pain and no pain) in other study⁴. This study observed neither the relation between gender and pain, nor duration of disease and pain.

Pathophysiology of PD primary pain is little understood, as well as the olfactory dysfunctions²⁹. The involvement of the dopaminergic system in pain transmission is still controversial. Presynaptic dysfunction of nigrostriatal dopaminergic pathway in burning mouth syndrome, suggested that the pathophysiology of this disease is the same for the pain in PD¹². Other possibility is that the physiopathological changes in the first pathways of pain transmission in the spinal dorsal cord described by Braak et al.¹⁵ lead to a pain in PD patients.

In summary, this study showed that the pain is a frequent complaint in PD patients. Stiffness might be a factor for the beginning of pain, but the tremor did not show this effect. However, there have been patients with pain in both on and off periods; probably these patients were in “wearing-off” status, requiring adjustment to medication. Neither dyskinesia nor depression was suggested relation to pain in PD. More than 50% of patients had improved under levodopa effect. Recognizing if the pain in PD is a primary or secondary condition, allows the adjustment of levodopa when necessary. In other situations, the use of analgesic, anti-inflammatory, antidepressant or anticonvulsive drugs, associated with physiotherapy permits a better quality of life to parkinsonian patients.

REFERENCES

1. Charcot JM. Lectures on diseases of the nervous system. London: Ed. The New Sydenham Society 1877;1:137.
2. Snider SR, Fahn S, Isgreen WP, Cote LJ. Primary sensory symptoms in parkinsonism. *Neurology* 1976;34:957-959.
3. Ford B. Pain in Parkinson's disease. *Clin Neurosci* 1998;5:63-72.
4. Goetz CG, Tanner CM, Levy M, Wilson RS, Garron DC. Pain in Parkinson's disease. *Mov Disord* 1986;1:45-49.
5. Quinn NP, Lang AE, Koller WC, Marsden CD. Painful Parkinson's disease. *Lancet* 1986;1:1366-1369.
6. Machteld EH, Sage JL. Nonmotor fluctuations in patients with Parkinson's disease. *Neurology* 1996;47:1180-1183.
7. Raudino F. Non motor off in Parkinson's disease. *Acta Neurol Scand* 2001;104:312-315.
8. Vaserman-Lehuédé N, Vérin Marc. Rhum [Engl Ed] 1999;66:220-223.
9. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. *Pain* 1995;60:3-38.
10. Nutt JG, Carter JH. Sensory symptoms in parkinsonism related central dopaminergic function [Letter]. *Lancet* 1981;345:2436-2437.
11. Ford B, Greene PG, Fahn S. Oral and genital tardive pain syndromes. *Neurology* 1994;44:2115-2119.
12. Clifford TJ, Warsi MJ, Burnett CA, Lamey PJ. Burning mouth in Parkinson's disease sufferers. *Gerodontology* 1998;15:73-78.
13. Pacchetti C, Albani G, Martignoni E, Godi L, Alfonsi E, Nappi G. “Off” painful dystonia in Parkinson's disease treated with botulinum toxin. *Mov Disord* 1995;10(Suppl 3):S333-S336.
14. Djaldetti R, Shifrin A, Rogowisk Z, Sprecher E, Melaned E, Yarnitsky D. Quantitative measurement of pain sensation in patients with Parkinson's disease. *Neurology* 2004;62:2171-2175.
15. Braak H, Sastre M, Bohl JRL, Vos RAL, Tredecí KD. Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic and sympathetic pre and postganglionic neurons. *Acta Neuropathol* 2007;113:421-429.
16. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55: 181-184.
17. Folstein MF, Folstein SF, McHugh PR. Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician *J Psychiatry Res* 1975;12:189-198.
18. Fahn S, Elton RL and members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB (Eds). *Recent development in Parkinson's disease*, New Jersey: Florham Park, 1987:153-163.
19. Pimenta CAM, Teixeira MJ. Avaliação da dor. *Rev Med* 1997; 76:27-35.
20. Beck AT, Ward CH, Mendelson M, Moc J, Erbaugh G. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4:53-63.
21. Koller W.C. Sensory symptoms in Parkinson's disease. *Neurology* 1984; 34:957-959.
22. Silva EG, Viana M, Quagliato EMAB. Pain in Parkinson's disease. *Arq Neuropsiquiatr* 2008;66:26-29.
23. Serrate G, Michel B. Pain in Parkinson's disease patients. *Rev Rhum [Engl Ed]* 1999;66:331-338.
24. Hageberg N, Forssell H, Rinne JO, et al. Striatal dopamine D1 and D2 receptors in burning mouth syndrome. *Pain* 2003; 101:149-154.
25. Hageberg N, Martikainen IK, Mansikka H, et al. A Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity. *Pain* 2002;99:273-279.
26. Starkstein SE, Preziosi TJ, Robinson RG. Sleep disorders, pain and depression in Parkinson's disease. *Eur J Neurol* 1991;31: 352-355.
27. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427-442.
28. Brefel-Courbon C, Payoux P, Thalamos C, et al. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord* 2005; 20:1557-1563.
29. Quagliato LB, Viana MA, Quagliato EMAB, Simis S. Alterações do olfato na doença de Parkinson. *Arq Neuropsiquiatr* 2007; 65:647-652.