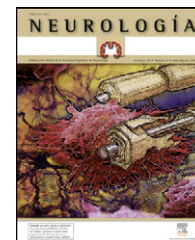




NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW ARTICLE

Central neuropathic pain in Parkinson's disease[☆]

C.B. Moreno, N. Hernández-Beltrán, D. Munévar, A.M. Gutiérrez-Alvarez^{*}

Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia

Received 4 April 2011; accepted 26 August 2011

Available online 30 October 2012

PALABRAS CLAVE

Dolor;
Dolor neuropático;
Enfermedad de
Parkinson;
Neurología;
Revisión sistemática;
Síntomas no motores

KEYWORDS

Neurology;
Neuropathic pain;
Non-motor
symptoms;
Pain;
Parkinson's disease;
Systematic review

Abstract

Introduction: Central pain is one type of pain that occurs in patients with Parkinson's disease (PD). Because of its low incidence and prevalence, it often goes unnoticed and affected patients do not therefore receive adequate analgesic therapy, which increases their suffering. It is a burning pain with spontaneous onset and periods of exacerbation; pain is poorly localised and usually more intense on the more affected side. Its pathophysiology on patients with PD is not clearly defined.

Methods: We performed a search and systematic selection of all clinical studies published from January 1986 to September 2010 concerning central neuropathic pain in Parkinson's disease.

Conclusions: Treatment with L-DOPA has not been demonstrated to have an analgesic effect on this type of pain. Future studies are required to improve our understanding of this condition, and to develop interventions for preventing and treating it.

© 2011 Sociedad Española de Neurología. Published by Elsevier España, S.L. All rights reserved.

Dolor neuropático central en enfermedad de Parkinson

Resumen

Introducción: El dolor central es uno de los tipos de dolor que se presentan en los pacientes con enfermedad de Parkinson (EP). Debido a que su incidencia y su prevalencia no son elevadas, con frecuencia pasa desapercibido y, por consiguiente, los pacientes afectados no reciben tratamiento analgésico adecuado, lo cual incrementa su padecimiento. Este dolor es de tipo quemante, de inicio espontáneo, con periodos de exacerbación, pobremente localizado y usualmente más intenso en el lado motor más afectado. Su fisiopatología aún no está claramente definida.

Desarrollo: Se realizaron una búsqueda y una selección sistemática de los estudios clínicos realizados en pacientes con EP, entre enero de 1986 y septiembre de 2010, que evaluaron el dolor neuropático central primario.

[☆] Please cite this article as: Moreno CB, et al. Dolor neuropático central en enfermedad de Parkinson. Neurología. 2012;27:500–3.

^{*} Corresponding author.

E-mail address: angelam.gutierrez@gmail.com (A.M. Gutiérrez-Alvarez).

Conclusiones: No se ha demostrado que el tratamiento con L-Dopa tenga efectos analgésicos sobre este dolor. Se requieren estudios futuros que permitan un mejor conocimiento de esta patología, para desarrollar mecanismos de prevención y tratamiento de esta enfermedad.
© 2011 Sociedad Española de Neurología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

Parkinson's disease (PD), the most common neurodegenerative movement disorder, affects approximately 1% of the population older than 65.¹ Its incidence rate is as high as 4% to 5% in subjects older than 85.² With a sex ratio of 1.5:1, it is more commonly found in men than in women.³ This disease is chronic and progressive, and its clinical manifestations vary considerably. Its first symptoms are rigidity, trembling, and bradykinesia; secondary symptoms may include shortened gait, dysarthria, and hypomimia. In addition, it presents with other non-motor symptoms that include cognitive impairment, sleep disorders, dysautonomia, and pain.

Pain is a cause of suffering and disability in PD patients. Unfortunately, it is often overlooked in clinical practice as the doctor tends to be more concerned about the patient's motor dysfunction.⁴ Prevalence of pain in PD patients varies between 40%⁵ and 83%.⁶ Back and neck pain have been described in early stages of the disease, and it may be caused by stiffness in the pectoral girdle. Leg pain may also be present and it can arise from restless leg syndrome or dystonia. In advanced stages, pain may be caused by dyskinesia, akathisia, off-period dystonia (40%) and non-dystonic musculoskeletal, articular, or radicular pain (20%),⁷ as James Parkinson so rightly described in his original article on "paralysis agitans".⁸

On the other hand, detailed questionnaires administered to patients revealed another type of complex pain in 10% to 30% of the total number of patients which could not be explained by the phenomena described above.⁹ These symptoms include deep burning or stabbing pains with stinging or tingling sensations in poorly defined areas of the body, generally on the side with the most motor impairment. Patients experience a mild sensation of tension and malaise which responds poorly to dopaminergic treatment and may precede classic parkinsonian symptoms.¹⁰ Central neuropathic pain as described above is considered a primary symptom, and it is the direct result of the illness and not of any musculoskeletal changes.¹¹

Neuropathic pain is pain originating directly from a lesion or illness that affects the somatosensory system. It is known as 'central' when its aetiology is found in the central nervous system.¹² The pathophysiological mechanisms of this type of pain in PD patients have not been established,¹³ and some suggest that it is caused by dysfunctional nociceptive processing in the central nervous system.^{11,14} This is supported by the decreased threshold for pain produced by heat stimuli in some of these patients.¹⁰ It could also be a change in pain modulation due to dopaminergic deficit in the basal ganglia-thalamocortical circuits.⁷

Although central neuropathic pain in PD was first described by Souques¹⁵ in 1921 as primary parkinsonian pain, this symptom has received little study. It is therefore necessary to examine its characteristics and treatment. This

article presents a systematic review of evidence in existing literature from studies that have evaluated primary central neuropathic pain in PD patients.

Method

We searched for and systematically selected clinical studies of PD patients which evaluated primary central neuropathic pain between January 1986 and September 2010. The search was performed using the Cochrane library, MEDLINE, EMBASE, and LILACS databases with combinations of the terms 'Parkinson', 'pain', and 'central pain' in both English and Spanish.

The search was completed electronically, after which we analysed the title and abstract content for the located articles. We then obtained full-text copies of any pertinent articles and reviewed all of the references included in those articles. With a view to identifying other relevant articles, we completed manual searches of the following journals: *Pain*, *Neurology*, *Lancet*, and *Movement Disorders*.

Results

We identified 10 articles^{6,10,13,16–22} on the topic of pain in PD patients. These studies included a total of 1111 patients with PD (and 390 healthy controls) in whom pain characteristics were evaluated. There were 5 case–control studies^{10,16–18,20} and 5 descriptive studies.^{6,13,19,21,22} Five articles were eliminated from the final review for one of the following reasons: not directly addressing patients with central pain (3 articles^{13,17,20}), not stating the number of patients with central pain or indicating whether central pain was primary or secondary (1 article²¹) and not describing pain characteristics for patients with central pain (1 article²²).

We analysed the case–control studies described below.

- In their study of 51 patients, Djaldetti et al.¹⁰ measured and compared perceived pain in 36 patients with unilateral PD with and without pain and in 15 patients with off-period fluctuations. It also included 28 healthy controls. This group used the visual analogue scale (VAS) to measure pain intensity. The threshold for tactile stimuli was measured using Von Frey hairs; pain and thermal sensation thresholds were measured using a Peltier module. Central neuropathic pain with burning and stinging sensations were present in 21 PD patients (8 women and 13 men). The threshold for pain caused by thermal stimuli was lower in PD patients than in the control groups. In turn, patients who experienced pain had significantly lower pain thresholds than PD patients without pain. Lastly, testing with thermal stimuli in the study revealed no differences between pain thresholds during

off-periods and on-periods for patients who experienced those fluctuations.

- Defazio et al.¹⁶ carried out a study of 402 PD patients and 317 controls. Pain frequency was significantly higher in patients with PD (281; 68.9%) than in controls (199; 62.8%). On the other hand, central neuropathic pain was more common in patients with PD (18; 4.5%) than in the control group (5; 1.6%). This association was found to be significant by logistic regression models examining pain presence, frequency, and type at the time of the study and in the 3 preceding months in both PD patients and age-matched control subjects. Regarding response to medication in the same study, there were no changes in neuropathic pain related to levodopa use.
- Schestatsky et al.¹⁸ studied pain perception in 9 patients (3 women and 6 men) with PD and central pain contrasted with that in 9 pain-free PD patients and 9 healthy controls. In these tests, they evaluated pain characteristics by using a quantitative sensitivity test with thermal probes. Laser-evoked potentials and laser-induced sudomotor responses were measured in both off-periods and on-periods. The researchers determined that during off-periods, patients with PD and central pain showed a lower threshold for pain produced by thermal stimuli, greater amplitude of laser evoked potentials, and less common laser-induced sudomotor skin responses compared to pain-free PD patients and healthy controls. Abnormalities were more noticeable on the affected side and tended to diminish after treatment with levodopa.

Although the descriptive studies we located have the limitations typical of their design, they deserve further mention.

Tinazzi et al.¹⁹ performed a retrospective study of the association of pain with motor complications in 117 patients (67 women and 50 men) with PD. Patients were asked if they had suffered any pain during the study period or in the 2 months prior to the study, and if so, what variables were associated with it; 47 patients (40%) comprising 28 women and 19 men reported pain. Central neuropathic pain was only identified in 2 patients who rated its intensity as 8 on the VAS scale; none showed signs of akathisia. Central pain in these 2 patients did not resolve with levodopa treatment.

Beiske et al.⁶ evaluated the clinical characteristics of pain suffered by 176 PD patients using a clinical examination and a structured interview, in addition to standardised questionnaires. It was determined that 146 patients (83%) reported pain as follows: musculoskeletal pain in 103 patients (70%), dystonic pain in 59 (40%), radicular neuropathic pain in 30 patients (20%), and central neuropathic pain in 15 patients (10%). The authors found no association between the presence of pain and patients' age, pain duration, or severity of the disease. The only significant predictor of pain was being female.

Discussion

Pain in PD patients is common, but it has not been thoroughly studied. Two types of pain have been described in these patients, and they are directly related to the disease. They are called dystonic and non-dystonic pain, depending

on whether or not they are caused by the musculoskeletal changes typical of the disease.¹⁶

Among pain types of non-dystonic origin, central neuropathic pain seems to be the least often studied, and it also frequently goes unnoticed. As a result, some patients do not receive sufficient analgesics. This review identified only 5 studies that describe pain characteristics in a total of 764 PD patients. Of that total, 65 (8.5%) were diagnosed as cases of primary central neuropathic pain.

The most common descriptions of central pain as provided by patients in 4 of the 5 studies are constant burning and itching sensations, normally located on the side with motor impairment (especially during off-periods) with no accompanying sensory deficit, and without pain being limited to a dermatome or a specific nerve distribution. The study by Defazio et al.¹⁶ mentions the diagnosis of central pain, but the authors do not describe the characteristics of this pain in any of their patients.

Although the cause of central pain in PD patients has not been defined, some suggest that changes in the extrapyramidal system may also produce changes in nociceptive information processing by the thalamus.¹⁰ It may also create abnormal neural circuits generating kindling-like pain, considering evidence that the basal ganglia participate in the control of discriminatory, cognitive, and affective aspects of nociception.^{23,24} According to this logic, patients with PD and pain have a significantly lower threshold for heat-produced pain stimuli than pain-free PD patients and healthy controls do.¹⁰

On the other hand, patients with PD and primary central pain have been shown to lack habituation to sympathetic sudomotor responses caused by repeated pain stimuli. This suggests changes in the control over harmful impulses in autonomic centres.¹⁸ However, other studies found no difference between the pain thresholds of PD patients with and without pain.

In the studies we revised, the relationship between central pain and on-periods and off-periods is unclear. Schestatsky et al.¹⁸ and Brefel-Courbon et al.²⁵ discovered that during off-periods, patients with PD and central pain had a lower threshold for pain caused by thermal stimuli. However, Djaldetti et al.¹⁰ did not find any such differences between on-periods and off-periods. Furthermore, positron emission tomography studies of pain-free PD patients during the off period revealed increased activation, caused by pain stimuli, of the right insular and prefrontal cortex and in the left cingulate cortex, compared to results from control subjects. This may suggest increased activation in central areas related to the processing of nociceptive information in PD patients. Researchers observed that administering L-DOPA to the same patients significantly reduced the activation described above.²⁵ However, other studies have not demonstrated any analgesic effect by L-DOPA in patients with PD and primary central pain. We therefore consider that this pain is caused by something other than a simple dopaminergic alteration.¹⁰

Conclusions

Central pain is one of the pain types that is present in PD patients. Its incidence and prevalence rates are not high and

it is frequently overlooked. As a result, patients affected by this type of pain do not receive the appropriate analgesic treatment, which increases their suffering. This pain appears as a burning sensation with sudden flare-ups. It is poorly localised and generally more intense on the side of the body with the most pronounced motor impairment. Treatment with L-DOPA has not been proven to have an analgesic effect on this type of pain.

The pathophysiology of primary central pain in PA patients remains undefined, but one hypothesis is an alteration in the control over the nociceptive system due either to a decrease in dopamine levels in basal ganglia or to abnormal neural circuits that create kindling pain. With the above in mind, future studies are needed in order to have a better understanding of this disease and improve care provided to patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Yang Y, Lu B. Mitochondrial morphogenesis, distribution, and Parkinson disease: insights from PINK1. *J Neuropathol Exp Neurol.* 2009;68:953–63.
2. Lang AE, Lozano AM. Parkinson's disease. First of two parts. *N Engl J Med.* 1998;339:1044–53.
3. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? *J Neurol Neurosurg Psychiatry.* 2004;75:637–9.
4. Ford B. Parkinson disease: pain in Parkinson disease: the hidden epidemic. *Nat Rev Neurol.* 2009;5:242–3.
5. Snider S, Fahn S, Isgreen W, Cote LJ. Primary sensory symptoms in parkinsonism. *Neurology.* 1976;26:423–9.
6. Beiske A, Svensson E, Ronningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. *Pain.* 2009;141:173–7.
7. Ford B. Pain in Parkinson's disease. *Clin Neurosci.* 1998;5:63–72.
8. Parkinson J. An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci.* 2002;14:223–36.
9. Quinn N, Koller W, Lang AE, Marsden CD. Painful Parkinson's disease. *Lancet.* 1986;1:1366–9.
10. Djaldetti R, Shifrin A, Rogowski Z, Sprecher E, Melamed E, Yarnitsky D. Quantitative measurement of pain sensation in patients with Parkinson disease. *Neurology.* 2004;62:2171–5.
11. Ford B. Pain in Parkinson's disease. *Mov Disord.* 2010;25:S98–103.
12. Treede R, Jensen T, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and grading system for clinical and research purposes. *Neurology.* 2008;70:1630–5.
13. Goetz CG, Tanner CM, Levy M, Wilson RS, Garron DC. Pain in idiopathic Parkinson's disease. *Mov Disord.* 1986;1:45–9.
14. Poewe W. Non-motor symptoms in Parkinson's disease. *Eur J Neurol.* 2008;15:14–20.
15. Souques MA. Des douleurs dans la paralysie agitante. *Rev Neurol (Paris).* 1921;37:629–33.
16. Defazio G, Berardelli A, Fabbrini G, Martino D, Fincati E, Fiaschi A, et al. Pain as a nonmotor symptom of Parkinson disease: evidence from a case–control study. *Arch Neurol.* 2008;65:1191–4.
17. Mylius V, Engau M, Teepker M, Stiasny-Kolster K, Schepelmann K, Oertel WH, et al. Pain sensitivity and descending inhibition of pain in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2009;80:24–8.
18. Schestatsky P, Kumru H, Valls-Sole J, Valldeoriola F, Martí MJ, Tolosa E, et al. Neurophysiologic study of central pain in patients with Parkinson disease. *Neurology.* 2007;69:2162–9.
19. Tinazzi M, Del Vesco C, Fincati E, Ottaviani S, Smania N, Moretto G, et al. Pain and motor complications in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2006;77:822–5.
20. Tinazzi M, Del Vesco C, Defazio G, Fincati E, Smania N, Moretto G, et al. Abnormal processing of the nociceptive input in Parkinson's disease: a study with CO₂ laser evoked potentials. *Pain.* 2008;136:117–24.
21. Lee MA, Walker RW, Hildreth TJ, Prentice WM. A survey of pain in idiopathic Parkinson's disease. *J Pain Symptom Manage.* 2006;32:462–9.
22. Hanagasi HA, Akat S, Gurvit H, Yazici J, Emre M. Pain is common in Parkinson's disease. *Clin Neurol Neurosurg.* 2011;113:11–3.
23. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. *Pain.* 1995;60:3–38.
24. Borsook D, Upadhyay J, Chudler EH, Becerra L. A key role of the basal ganglia in pain and analgesia—insights gained through human functional imaging. *Mol Pain.* 2010;6:27.
25. Brefel-Courbon C, Payoux P, Thalamas C, Ory F, Quélven I, Chollet F, et al. Effect of Levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord.* 2005;20:1557–63.