Parkinson’s disease related pain: a review of recent findings

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Abstract In this review we summarize progress in research on Parkinson’s disease-related pain as reported in articles published in the Journal of Neurology in the years 2011 and 2012.

Keywords Neuropathic pain · Central pain · Parkinson disease

Introduction

As well as the well-known motor symptoms, patients with Parkinson’s disease (PD) commonly experience pain [1]. Published studies indicate a prevalence ranging from 40 to 85 % (mean 67.6 %) [2]. Pain severely impairs parkinsonian patients’ quality of life and some patients find this non-motor symptom more distressing than motor disturbances.

Like motor symptoms, non-motor symptoms including pain arise through mechanisms involving nociceptive inputs to the basal ganglia [3]. Animal experiments show that morphine microinjected into the striatum and substantia nigra produces a naloxone-reversible analgesia unrelated to motor function [4]. In rats with experimentally-induced painful neuropathy striatal activity increased and opioids suppressed this increase [5]. Nociceptive inputs travel to the striatum from the various pain-related cortical areas including SII, insula, cingulate cortex, prefrontal areas, andthalamic intralaminar nuclei [6]. The nociceptive-responsive striatal neurons have large receptive fields and strongly respond as the noxious input increases in intensity, thus suggesting that rather than spatially localizing pain the striatum codes its nociceptive input intensity [7]. The basal ganglia also connect with several pain-related areas. Substantia nigra efferent pathways connect to amygdala, prefrontal cortex and cingulate cortex, areas involved in the motivational-affective pain dimension [8]. Neuroimaging studies in humans show that pain modulation involves striatal dopamine D2 receptors [9]. All these data suggest that abnormal basal ganglia function in PD modulates pain directly by increasing or diminishing nociceptive signal propagation, and indirectly by influencing affective and cognitive processes thereby regulating how patients expect, experience and interpret nociceptive signals and pain.

Patients with PD experience two different types of pain, nociceptive and neuropathic. Nociceptive pains are extremely frequent (accounting for 40–90 % of reported pain) [1]. Nociceptive pain related to PD is typically musculoskeletal and visceral. Musculoskeletal pain usually originates from abnormal posture, rigidity, and akinesia causing motor fluctuations, thus leading to painful dystonia. The most typical painful dystonia, reported by about 40 % of patients with PD, is that manifesting in the early morning, when dopaminergic stimulation is low and akinesia and rigidity are severe. Early morning dystonia manifests as a focal dystonia with plantar flexion and foot inversion. Another frequent type of nociceptive pain is the visceral pain that frequently accompanies constipation. Bowel functioning in patients with PD depends on several factors including autonomic failure involving the enteric nervous system. Dystonic contractions involving the anal sphincter can cause painful anismus.

PD-related neuropathic pain comprises radicular pain and central Parkinson’s pain. Radicular pain has a higher prevalence in patients with PD than in the general population (14–35 % vs. 10 %) [1, 10]. This high frequency
probably reflects the lumbar discal structure damage due to
festination, kyphosis and dystonia. Pain directly related to
PD (central Parkinson’s pain) is a relatively rare condition
(4–10 % of patients) [1, 11]. It mainly affects the body side
with predominant motor symptoms and patients usually
describe it as a burning, cramping sensation. Unlike
“classic” central pain, central Parkinson’s pain has no
association with the clinically evident sensory deficits that
reflect afferent pathway damage [12]. Although the data
argues against the currently accepted criteria for defining
neuropathic pain given that the diagnosis requires a sensory
deficit, most investigators believe that this type of pain
arises directly from basal ganglia dysfunction that alters
sensory processing of nociceptive inputs [1, 11].

Over the past 2 years interest in problems related to pain
in PD has enormously increased. This article reviews and
summarizes the new findings in PD-related pain published
in the Journal of Neurology in the years 2011 and 2012.

Clinical information on pain related to PD

Virtually all patients with PD have non-motor symptoms,
the most frequent being psychiatric symptoms and pain
[13]. Non-motor symptoms may even, though rarely, pre-
cede the onset of the typical motor disorders. This pre-
motor stage reflects the early structural changes taking
place in the lower brainstem nuclei and peripheral nervous
system, including the autonomic and enteric ganglia.
Identifying the pre-motor stage could be clinically useful,
because early treatment might influence the disease course,
improving the long-term outcome. Pain is one of the most
common pre-motor symptoms of PD, and can affect the
patient’s life for years before PD is diagnosed. In their
study highlighting the importance and high frequency of
pain as a non-motor symptoms, Winkler and colleagues
[14] proposed a PD risk score, grading various non-motor
items including pain to define a risk profile for identifying
patients with PD who might benefit from disease-modify-
ing strategies. Whether managing PD early implies a better
outcome also in non-motor symptoms, such as pain, is an
open matter. To answer the question we need studies
designed to assess the PD-related pain burden in relation-
ship to disease-modifying drugs and treatment timing.

Although most studies report that PD-related pain is
significantly more frequent in women than in men [11],
some articles state the contrary [15]. Aiming at analysing
the gender differences in non-motor PD symptoms,
including pain, Martínez-Martín and colleagues studied for
study 950 patients with PD [16]. Using the Non-Motor
Symptom Score they investigated 30 items, including pain.
Whereas no differences were found in age, age at onset,
duration of disease, and motor disability between genders,
pain was significantly more frequent in women than in men. This gender-related difference in pain in PD is in line
with the many epidemiological studies showing that vari-
ous acute and chronic pains, such as headache, oro-facial,
musculoskeletal and abdominal pains are more frequent in
women than in men. Although some sex-related differences
in pain might reflect cognitive and social factors, the lower
pain threshold and pain tolerance in women might arise
partly from biological differences. Several experimental
studies have documented gender differences in opioid
analgesia suggesting that the endogenous pain inhibitory
system is less efficient in women than in men [17]. The
gender differences in PD-related pain, reported in the study
by Martin and colleagues, could be used to improve pain
management in PD for both genders, and analyze gender-
related differences in outcome after similar treatments.

Although many studies show that PD-related pain
adversely influences patients’ quality of life [18, 19], no
study has investigated how pain affects daily activities. The
study by Trail and colleagues [20], examining the rela-
tionships among activity and daily energy expenditure,
non-motor symptoms and body mass index, surprisingly
demonstrates that pain affects patients’ daily activities
more than their memory problems and depression.
Although this study admirably highlights the pain burden
in daily activity in PD, unfortunately, because it was con-
ducted in a veteran’s hospital, it almost exclusively
enrolled men (98 %). Because pain is more frequent and
severe in women than in men [21], this collection bias
might weaken the study’s clinical significance on the
impact of pain in patients with PD.

Managing PD and its related non-motor symptoms,
including pain, exacts a considerable economic burden,
especially given worldwide population aging. Intense
research efforts, therefore, focus on reducing costs by
developing new treatments and models for care. These
developments oblige the national reimbursement agencies
to undertake an accurate cost-effectiveness analysis.
Although many studies have examined how non-motor
symptoms and pain influence quality of life, little is known
about health state utility values (the measure used in health
economics for assessing the individual’s preferences for
different health outcomes). In their study [22] in patients
with a recently diagnosed PD, Shearer and colleagues have
investigated health state utility values and estimated their
clinical and demographic correlates for future economic
studies. Besides providing data useful for cost-effectiveness
analysis the investigators also report that pain can
have a greater impact on quality of life than motor symp-
toms, thus underlining how important it is to manage non-
motor symptoms more effectively in newly diagnosed PD.

Although the many studies addressing the problem of
non-motor symptoms in PD have reported their high
frequency and clinical importance, they used only short-term prospective observation periods. Hence, we know little about how these symptoms progress and how they contribute to deteriorating quality of life during the disease course. As the disease progresses, rigidity and akinesia producing musculoskeletal abnormalities and fluctuating motor symptoms causing painful dystonia (such as the early morning dystonia) increase [23]. Hence, the frequency and severity of pain should increase in parallel. The large prospective PRIAMO study (Parkinson’s and nonmotor symptoms) [24] collecting 707 patients and assessing symptoms related to 12 different non-motor domains over 24 months reports that as overall non-motor symptoms increase in number along with disease motor severity and duration. But whereas some domains such as sleep, gastrointestinal symptoms, attention/memory disturbances and skin disorders (hyperhidrosis and seborrhoea) become more prevalent, psychiatric, cardiovascular, and respiratory symptoms become less prevalent. Unexpectedly, the frequency and clinical importance of pain remained basically stable. The study reported that the number of patients complaining of pain increased by only 1%, and the 39-item Parkinson’s Disease Questionnaire (PDQ-39), the scale used for quality of life assessment [25] remained unchanged. Although this study provides the previously unavailable information on how pain influences disease progression and quality of life in PD it has two important limitations. It fails to assess symptom severity, or take medications into account. One reason why the study by Antonini et al. [23] found no significant differences in pain incidence might be that patients changed the pain-killers or antiparkinsonian medications they used during the study. Consistently, in most patients (more than 80%) the Hoehn and Yahr scale remained unchanged during follow-up, thus suggesting stable motor control, probably because pharmacological treatment changed during the course of the disease. Further studies investigating pain progression should probably include data for medications used in their results.

**Pathophysiology**

Whereas animal studies underline the role of the basal ganglia and dopaminergic transmission in pain, the mechanisms underlying pain related to PD in humans remain unclear. Currently only indirect evidence suggested nociceptive system dysfunction in patients with PD. The study by Zambito and colleagues [26] adds information on how PD can put patients at higher risk of pain than healthy subjects. Using electrical stimulation they assessed tactile threshold, pain threshold, and pain tolerance in 106 PD patients (66 of whom had chronic pain). They found that pain threshold and pain tolerance were significantly lower in PD patients than in control subjects, whereas tactile threshold values were comparable in both groups. Surprisingly pain threshold and pain tolerance tend to lower as PD progresses, thus suggesting that as basal ganglia dysfunction worsens, nociceptive system involvement increases. Unexpectedly no difference was found in pain thresholds and pain tolerance between PD patients with and without pain. This finding seems to argue against the possibility that decreased sensory thresholds play some role in the development of pain in PD patients, but when Zambito et al., analyzed sensory thresholds they failed to distinguish between neuropathic and nociceptive pain. This distinction is important because whereas nociceptive pain is presumably unrelated to changes in sensory thresholds, neuropathic pain, a pain type that directly involves the nociceptive pathways, is associated with abnormal sensory thresholds [27].

**Treatment options**

The treatment of PD-related pain hinges on empirical data alone and no large randomized controlled data are available. The pharmacological management relies on antiparkinson, antinociceptive and antineuropathic medications. Deep brain stimulation (DBS) targeted to the subthalamic nucleus and globus pallidus, a surgical procedure widely used for treating motor disorders in PD [28, 29], effectively relieves various types of PD-related pain, such as musculoskeletal, dystonic and central Parkinson pain [30, 31]. Despite these successful DBS applications in their prospective study, Capelle and colleagues [32] showed that DBS targeted to the subthalamic nucleus and globus pallidus has only a mild and negligible effect on an unusual type of PD-related pain: the back pain due to camptocormia (the rare and disabling condition provoking abnormal trunk flexion). This finding implies that this condition, unlike segmental dystonia, arises through other still unknown mechanisms, insensitive to DBS. The study conducted by Capelle et al. provides useful information indirectly supporting the idea that PD-related pain is a heterogeneous condition arising through multiple and diverse mechanisms, and may help in defining a PD pain profile that responds to DBS [33].

**Conclusions and future directions**

Studies dealing with PD-related pain published in the Journal of Neurology over the past 2 years highlighting the importance of pain in PD have provided new insights into this common problem. Despite advancing our knowledge in this field they leave many questions open. Most
important, how should we categorize PD-related pain? Few studies reliably distinguish the various types of PD-related pain. Because the various types of pain arise from different mechanisms, and probably respond differently to treatment [34], the major need is to classify pain according to its pathophysiological mechanisms and use the information to plan reliable pharmacological trials.

Although no randomized controlled trials have yet investigated PD-related pain, some pharmacological and non-pharmacological trials are now underway (www.investigated PD-related pain, some pharmacological and plan reliable pharmacological trials.

pathophysiological mechanisms and use the information to advances for patients with PD.

Conflicts of interest The authors have no conflict of interest to declare.

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References

1. Wasner G, Deuschl G (2012) Pains in Parkinson disease—many syndromes under one umbrella. Nat Rev Neurol 17(8):284–294
2. Broen MP, Braakasma MM, Patijn J, Weber WE (2012) Prevalence of pain in Parkinson’s disease: a systematic review using the modified QUADAS tool. Mov Disord 27(4):480–484
3. Schapira AH (2011) Aetiopathogenesis of Parkinson’s disease. J Neurol 258(Suppl 2):S307–S310
4. Anagnostakis Y, Zis V, Spyraki C (1992) Analgesia induced by morphine injected into the pallidum. Behav Brain Res 48(2):135–143
5. Beck T, Wenzel J, Kuschinsky K, Krieglstein J (1989) Morphine-induced alterations of local cerebral glucose utilization in the basal ganglia of rats. Brain Res 497(2):205–213
6. Pay S, Barasi S (1982) A study of the connections of nociceptive substantia nigra neurones. Pain 12(1):75–89
7. Richards CD, Taylor DC (1982) Electrophysiological evidence for a somatotopic sensory projection to the striatum of the rat. Neurosci Lett 30(3):235–240
8. Burkey AR, Carstens E, Jasmin L (1999) Dopamine reuptake inhibition in the rostral agranular insular cortex produces antinociception. J Neurosci 19(10):4169–4179
9. Hagelberg N, Jääskeläinen SK, Martikainen IK, Mansikka H, Forssell H, Scheinin H, Hietala J, Pertovaara A (2004) Striatal dopamine D2 receptors in modulation of pain in humans: a review. Eur J Pharmacol 500(1–3):187–192
10. Broetz D, Eichner M, Gasser T, Weller M, Steinbach JP (2007) Radicular and nonradicular back pain in Parkinson’s disease: a controlled study. Mov Disord 22:853–856
11. Beiske AG, Loge JH, Ronningen A, Svensson E (2009) Pain in Parkinson’s disease: prevalence and characteristics. Pain 141:173–177
12. Truini A, Barbanti P, Pozzilli C, Crucu G (2012) A mechanism-based classification of pain in multiple sclerosis. J Neurol Jul 4
13. Park A, Stacy M (2009) Non-motor symptoms in Parkinson’s disease. J Neurol 256(Suppl 3):293–298
14. Winkler J, Ehret R, Büttner T, Dillmann U, Fogel W, Sabolek M, Winkelmann J, Kassubek J (2011) Parkinson’s disease risk score: moving to a premonitory diagnosis. J Neurol 258(Suppl 2):S311–S315
15. Ha AD, Jankovic J (2012) Pain in Parkinson’s disease. Mov Disord 27(4):485–491
16. Martinez-Martin P, Falup Pecurariu C, Odin P, van Hiltgen JJ, Antonini A, Rojo-Abuin JM, Borges V, Trenkwalder C, Aarsland D, Brooks DJ, Ray Chaudhuri K (2012) Gender-related differences in the burden of non-motor symptoms in Parkinson’s disease. J Neurol 259(8):1639–1647
17. Bernal SA, Morgan MM, Craft RM (2007) PAG mu opioid receptor activation underlies sex differences in morphine antinociception. Behav Brain Res 177(1):126–133
18. Visser M, van Rooden SM, Verbaan D, Marius J, Stiggelbout AM, van Hiltgen JJ (2008) A comprehensive model of health-related quality of life in Parkinson’s disease. J Neurol 255(10):1580–1587
19. Winter Y, von Campenhausen S, Gasser J, Seppi K, Reese JP, Pfeiffer KP, Bötzel K, Oertel WH, Dodel R, Poewe W (2010) Social and clinical determinants of quality of life in Parkinson’s disease: a cohort study. J Neurol 257(4):638–645
20. Trail M, Petersen NJ, Nelson N, Lai EC (2012) An exploratory study of activity in veterans with Parkinson’s disease. J Neurol 259(8):1686–1693
21. Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, Gold MS, Holdcroft A, Lautenbacher S, Mayer EA, Mogil JS, Murphy AZ, Traub RJ, Consensus Working Group of the Sex, Gender, and Pain SIG of the IASP (2007) Studying sex and gender differences in pain and analgesia: a consensus report. Pain 132(Suppl 1):S26–S45
22. Shearer J, Green C, Counsell CE, Zajicek JP (2012) The impact of motor and non motor symptoms on health state values in newly diagnosed idiopathic Parkinson’s disease. J Neurol 259(3):462–468
23. Gershankis OS (2010) Clinical problems in late-stage Parkinson’s disease. J Neurol 257(2):S288–S291
24. Antonini A, Barone P, Marconi R, Morgante L, Zappulla S, Pontieri FE, Ramat S, Ceravolo MG, Meco G, Cicarelli G, Pedrizzol M, Manfredi M, Ceravolo R, Mucchiut M, Volpe G, Abbruzzese G, Botaacchi E, Bartolomei G, Cannas A, Randisi MG, Petrone A, Benetti M, Toni V, Cosso G, Del Dotto P, Bentivoglio AR, Abrisgnani M, Scala R, Pennisi F, Quattrale R, Guglielmo RM, Nicolletti A, Perini M, Avarelo T, Pissani A, Scaglioni A, Martellini PE, Iemolo F, Ferigo L, Simone P, Soliveri P, Troianiello B, Consoli D, Mauro A, Lopiano L, Nastasi G, Colosimo C (2012) The progression of non-motor symptoms in Parkinson’s disease and their contribution to motor disability and quality of life. J Neurol Jun 19
25. Martinez-Martin P, Frades Payo B (1998). Quality of life in Parkinson’s disease: validation study of the PDQ-39 Spanish version. The Grupo Centro for Study of Movement Disorders. J Neurol 245(1):S34–S38
26. Zambrano Marsala S, Tinazzi M, Vitaliani R, Recchia S, Fabris F, Marchini C, Fiaschi A, Moretto G, Giometto B, Maccarone A, Defazio G (2011) Spontaneous pain, pain threshold, and pain tolerance in Parkinson’s disease. J Neurol 258(4):627–633
27. Treede RD, Jensen TS, Campbell JN, Crucu G, Ostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmiikko T, Serra J (2008) Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 70(18):1630–1635
28. Antonini A, Pilleri M, Padova A, Landi A, Ferla S, Biundo R, D’Avella D (2012) Successful subthalamic stimulation in genetic Parkinson’s disease caused by duplication of the α-synuclein gene. J Neurol 259(1):165–167
29. Fasano A, Daniele A, Albanese A (2012) Treatment of motor and non-motor features of Parkinson’s disease with deep brain stimulation. Lancet Neurol 11(5):429–442

30. Kim HJ, Paek SH, Kim JY, Lee JY, Lim YH, Kim MR, Kim DG, Jeon BS (2008) Chronic subthalamic deep brain stimulation improves pain in Parkinson disease. J Neurol 255(12):1889–1894

31. Zahodne LB, Okun MS, Foote KD, Fernandez HH, Rodriguez RL, Wu SS, Kirsch-Darrow L, Jacobson CE 4th, Rosado C, Bowers D (2009) Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. J Neurol 256(8):1321–1329

32. Capelle HH, Schrader C, Blahak C, Fogel W, Kinfe TM, Baezner H, Krauss JK (2011) Deep brain stimulation for camptocormia and Parkinson’s disease. J Neurol 258(1):96–103

33. Wächter T, Mínguez-Castellanos A, Valldeoriola F, Herzog J, Stoevelaar H (2011) A tool to improve pre-selection for deep brain stimulation in patients with Parkinson’s disease. J Neurol 258(4):641–646

34. Truini A, Biasiotta A, La Cesa S, Di Stefano G, Galeotti F, Petrucci MT, Inghilleri M, Cartoni C, Pergolini M, Cruccu G (2010) Mechanisms of pain in distal symmetric polyneuropathy: a combined clinical and neurophysiological study. Pain 150(3):516–521