

Mini Review

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Mini review – Clinical and physiological aspects of pain in parkinson's disease

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ABSTRACT

Pain is a common and often disabling symptom in Parkinson's disease (PD) which has received increasing attention in recent years. Headache represents a common form of pain among the general population, but there are few studies on this symptom in PD. In 2014, our group reported a lower prevalence of headache in PD patients compared to the general population, as well as an association between the predominant side of headache and the side of initial motor signs of PD. Since then, there has been few new data on the specific issue of headache in PD patients, though several recent studies have contributed to the understanding of pain in PD, both in terms of clinical and pathophysiological aspects, including new observations on pain association with side of motor symptom onset. Here, we review those studies, and re-discuss our own findings in comparison to the current information available. A better comprehension of pain physiology in PD could facilitate the development of new therapeutic approaches, thus providing a better quality of life for PD patients.

Introduction

Pain is a common and often disabling symptom in Parkinson's disease (PD)¹. Headache represents a common form of pain, but there are few studies about headache in PD². In an article published in 2014, we reported the prevalence and characteristics of headache in 100 consecutive PD patients². They were compared to 98 age- and gender-matched controls from a Brazilian population-based epidemiological study^{2,3}. We found a statistically significant lower prevalence of headache in PD patients. It was also shown that, when the PD patients' headache was unilateral, its predominant side was ipsilateral to the side of initial motor signs of PD, with 84% concordance ($p < 0.01$)².

Although the study design did not allow a cause-effect relationship, we hypothesized that this association could be explained by some protective effect of PD against headache. Since then, many works have addressed the issue of pain in PD⁴⁻¹⁷. Here, we reviewed the new findings about pain in PD, and re-discuss our hypothesis in the light of the current information.

Pain in Parkinson's disease

Pain in PD is frequent^{1,4-6}, can be disabling¹ and have an important impact on the patients' quality of life⁴. Pain is reported among the symptoms of PD since the earliest publications on the subject, and

Reference	Musculoskeletal %	Radicular/neuropathic %	Dystonic %	Central/primary %	Akathisia %
Valkovic P et al ⁴	41.0	27.0	17.0	22.0	a
Rana A et al ⁵	28.0	36.0	48.0	b	29.0
Mao CJ et al ⁶	47.1	19.1	23.5	7.4	2.9

^aReference⁴ did not assess akathisia

^bReference⁵ did not describe the prevalence for central/primary pain

Table 1: Relative frequency of each category of pain in Parkinson's disease (Ford's classification).

is noted for being capable of overshadowing the motor symptoms of the disease¹. A recent study reported a significant association between pain and poorer quality of life and more severe depression in PD patients⁴. Therefore, pain emerges as an important non-motor symptom (NMS) of PD, albeit an often overlooked one¹.

In order to provide better diagnosis and comprehension of pain in PD, several pain classification systems in PD have been designed⁴, of which the system proposed by Ford¹ remains the most cited⁴. The author classified pain in PD in five categories: musculoskeletal, radicular/neuropathic, dystonic, central/primary and akathisia¹. According to this system, PD-related headache is classified as central/primary pain¹. This scheme was used in several papers reviewed here⁴⁻⁶, and the relative frequency of each category of pain is exposed in Table 1.

Prevalence studies

Although no new published research has specifically assessed the frequency and characteristics of headache in PD, many studies in recent years have investigated the prevalence of pain among PD patients and factors that could be related to its occurrence⁴⁻⁶. Valkovic et al. reported a 76.0% prevalence of overall pain (OP) among PD patients in a cross-sectional study, though headache was not referred in this population⁴. OP was found to be worse in patients with advanced PD, with patients with advanced disease reporting more frequently musculoskeletal, radicular/neuropathic, dystonic and central/primary pain⁴. Patients with early PD reported more frequently pain that could not be classified under those categories, thus being put under the label "other pain"⁴. A Canadian study identified a prevalence of 66.0% of OP⁵. Severity of PD showed no association with OP level⁵. Mao et al. investigated possible associations between PD-related OP and other NMS⁶. They reported a prevalence of OP among PD cases of 47.9%, and observed that PD patients with pain had more severe PD and scored higher in a depression questionnaire and lower in cognitive tests, with statistical significance⁶. In 2014, clinical differences between 39 PD patients with mutations in the glucocerebrosidase gene (GBA) and 539 sporadic PD controls were compared⁷. Four patients with GBA-associated PD and 16 controls with sporadic PD presented with OP as an initial symptom⁷. A single study evaluated OP in PD, multiple system atrophy (MSA) and progressive

supranuclear palsy (PSP), reporting a greater prevalence in PD and MSA in comparison to PSP (89.0%, 81.0% and 25.0%, respectively), as well as a lower intensity of OP in PSP⁸.

Neurotransmitter studies

Tong et al⁹ found an inverse association between plasmatic levels of serotonin and 5-hydroxyindoleacetic acid and OP among PD patients, as well as lower plasmatic levels of both substances in PD patients when compared to healthy controls, and proposed that serotonergic dysfunction could play a role in PD, particularly in the genesis of NMS like pain⁹. This research group had published an article one year earlier, investigating a possible correlation between PD NMS and plasmatic levels of glutamate, aspartate, γ -aminobutyric acid and glycine but, despite having found associations between plasma amino acids and depression and sleep disturbances, there was no significant correlation to OP¹⁰.

Neurophysiologic studies

One study using a quantitative technique to measure fiber-selective sensory thresholds compared the current perception and pain tolerance thresholds (CPT and PTT, respectively) between PD patients and controls¹¹. CPT represents the intensity of an electrical stimulus at which the subject becomes aware of its presence, while PTT represents the intensity of such stimulus above which the subject perceives such stimulus as intolerable pain¹¹. The method applied by the authors allows discrimination between A β -, A δ - and C-fiber CPT and PTT¹¹. It showed, with statistical significance, that patients had higher CPT for all three types of fibers and lower PTT for A β and A δ fibers than controls. Patients who reported painful symptoms had statistically significant higher A δ - and C-fiber CPT than those without pain. PD subjects with OP also had lower PTT, though without statistical significance¹¹. These findings have led the authors to propose a role for abnormal sensory inputs in the pathogenesis of pain in PD¹¹.

Another study applied a well-established conditioned pain modulation (CPM) paradigm to 25 PD patients and 30 controls¹². The paradigm combined painful heat stimuli and a cold pressor task as the conditioning stimulus¹². No significant differences between both groups in pain modulation were found, and no significant effect of levodopa

on CPM was shown¹². Once CPM evaluates the efficacy of descending pain inhibition mechanisms, the authors concluded that PD is not associated with impairment of endogenous pain inhibition beyond the age-related decline¹².

Studies with animal models

Maegawa et al. analyzed the effects of nigrostriatal pathway lesions on nociception using a PD murine model¹³. Face rubbing in rats with chemical lesion of the left medial forebrain bundle was compared to that of control rats after nociceptive stimulus to the upper lip. Between 10 and 90 minutes after the stimulus, face rubbing was larger in PD-model rats¹³. From these data, it was inferred that nigrostriatal damage resulted in hypersensitivity to chemical painful stimulation. The authors suggested that dopamine may play a role in the modulation of inflammatory pain and central sensitization¹³.

Pain lateralization in Parkinson's disease

Our work reported a significant positive association between side of PD motor symptom onset and side of headache in those patients who reported unilateral headache². Similarly, Rana et al. found an association between right-sided pain and PD motor symptoms onset on the right side⁵. Interestingly, such a relationship was not observed with left-sided pain⁵. Kresojević detected a high concordance between side of motor symptom onset and side of OP was high among the subjects who reported pain, with all 4 GBA cases and 14 out of 16 controls having OP localized to the upper limb ipsilateral to the motor symptoms onset, but the study only assessed pain as an initial symptom, and the number of PD patients who reported pain as the presenting symptom was small (20), and inferential analysis on this issue was not performed⁷. The study with PD-model rats has also addressed this issue, revealing that PD-model rats showed hypersensitivity to painful stimuli, particularly worse ipsilaterally to the nigrostriatal involvement¹³.

In contrast, Mao found no significant relationship between side of motor symptom onset and side of OP⁶. Also, in the work of Chen, no association between sensory function or pain tolerance and the side of more severe motor symptoms was detected¹¹.

Though the data available are limited and the methods employed in different studies vary, some studies have observed that pain syndromes occur more frequently in the same side as the motor symptoms in PD.

Dopaminergic therapy and pain

Rana did not find any significant associations between presence of dopaminergic therapies (DT) and pain scores, though 40% reported subjective improvement with the medication⁵. Similarly, in Mao's work the daily equivalent

dose of levodopa of the patients with OP was not higher than that of those without OP⁶. One study showed rates of subjective improvement of OP after DT of 51.0%, 57.0% and 25.0% for PD, MSA and PSP, respectively⁸. CPT and PTT were not affected by DT¹¹, and DT did not influence CPM¹². A proper comparison of these studies in regard to a possible effect of DT on pain in PD is difficult, because the methods and study designs are heterogeneous. Nonetheless, most of them suggest DT has no objective effect on pain. A randomized controlled trial of DT in PD having as primary outcome the reduction of OP would perhaps clarify this issue.

The effects of deep brain stimulation on pain in Parkinson's disease

Deep brain stimulation (DBS) has emerged as an effective treatment for motor symptoms of PD¹⁴. Its impact on NMS of PD has been increasingly investigated, providing new insights into the pathophysiology of pain in PD.

A cohort followed 41 PD patients who underwent subthalamic nucleus DBS (STN-DBS), assessing OP and NMS before and one year after surgery¹⁴. An improvement of OP after STN-DBS was shown, particularly of dystonic and musculoskeletal pain¹⁴. Neuropathic and central pain were not influenced by the procedure¹⁴. The authors did not find any association between motor symptom improvement and OP reduction after STN-DBS¹⁴. A previous study with a similar design had found a significant reduction of sensory and affective aspects of pain in a sample of 58 PD patients after STN-DBS, and that effect was independent of motor improvement¹⁵. Another work followed and evaluated OP in PD patients for 8 years after STN-DBS, documenting an improvement of OP in all 24 subjects, though no objective method for pain intensity quantification was employed¹⁶. It also reported that 3 out of 24 selected PD patients had headache¹⁶. A cohort published in 2015 reported an improvement of OP and lower back pain in PD patients after STN-DBS¹⁷.

It has been consistently shown that STN-DBS may reduce OP¹⁴⁻¹⁷, and that effect seems to be independent of the procedure's benefit on parkinsonian motor symptoms^{14,15}. Once DBS mainly acts on the nigrostriatal pathways via STN stimulation, thus increasing thalamocortical excitation, it seems plausible that basal ganglia may play a direct role in pain modulation.

Conclusion

Even with a high prevalence of OP among PD patients^{4,6}, headache itself does not seem to be a common complain^{4,16}. That is in accordance with our case-control study, in which a lower occurrence of headache was observed in PD subjects². Both headache and OP may be more frequently ipsilateral to motor symptoms in PD^{2,5,7,13}, though study

results are conflicting and data are lacking to make a definite assumption.

The genesis of pain in PD may be more related to abnormal sensory input pathways¹¹ than to impaired pain-inhibiting mechanisms¹². In the animal model of PD, nigrostriatal damage was shown to produce central sensitization¹³. Serotonergic dysfunction may also be involved in the pathophysiology of pain in PD⁹.

Although the analysis of DT on pain in PD did not show any significant association^{5,6,8,11}, STN-DBS was shown to reduce pain in PD¹⁴⁻¹⁷, and that reduction seems to be independent of the benefit of DBS on motor symptoms^{14,15}. Once STN-DBS increases thalamocortical activation, these findings could mean that the basal ganglia may participate in pain modulation mechanisms that, when dysfunctional, could lead to the generation of pain in PD independently of motor symptoms.

The reason why headache is so uncommon in PD despite the high frequency of OP is still elusive. PD impairment of pain modulation circuits may be selective for certain painful syndromes, increasing the occurrence of certain kinds of pain while decreasing others. Data about headache in PD is scarce and more comprehensive and high-quality descriptive studies are necessary in order to better characterize this symptom and its occurrence in PD. Conversely, studies employing functional imaging to compare PD patients and controls in regard to patterns of brain activation to painful stimuli could promote a better comprehension of the mechanisms through which PD affects pain modulation.

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