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EFFECTS OF PAIN ON ACTIVITIES OF DAILY LIVING AND FUNCTIONING IN PARKINSON'S DISEASE PATIENTS

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Abstract

Objective: To investigate how pain affects Parkinson's disease (PD) patients in their activities of daily living (ADL) and functioning, and to identify correlations among ADL and types of pain, pain locations, and demographics.
Methods: The study population comprised 104 PD patients who reported feeling pain. Patients indicated whether pain affected particular actions, including standing, walking, and laboring. Patients further reported the functional effects of pain on their emotional and social health. Data was collected using self-made questionnaires.
Results: Overall, akathisic pain was the most effective predictor of negative effects of pain on ADL. The presence of akathisic pain increased the likelihood of mobility problems by almost 4.0-fold ($p = 0.024$), exhaustion by 10.0-fold ($p = 0.017$), social functioning problems by 3.5-fold ($p = 0.037$), lack of enjoyment in life by approximately 4.0-fold ($p = 0.017$) and problems in emotional functioning by 3.6-fold ($p = 0.025$). In addition, it was found that the duration of PD was correlated to problems with daily work ($p = 0.033$); Hoehn and Yahr stage of PD at diagnosis was correlated to exhaustion ($p = 0.013$); and male gender was correlated to a lack of perceived enjoyment of life ($p = 0.010$).
Conclusion: Pain is a debilitating symptom of PD patients, and has a negative impact on ADL. Thus, medical professionals should seriously consider the effects of pain in deciding the optimum therapeutic approach for PD patients.

Keywords
• Activities of daily life • Parkinson's disease • Pain • Functional outcome

Introduction

Classification of pain in PD

Over 90% of Parkinson's disease (PD) patients experience non-motor symptoms. Of these, pain has been shown to be one of the most common and significant [1]. The presence of pain in PD patients is supported by various case-control studies, which aimed to compare the incidence of pain in PD patients to that of the healthy population [2]. Approximately 30% to 85% of patients with PD complain of experiencing pain [3]. Painful symptoms can be categorized as either primary or secondary in nature. These groups can be further subdivided on the basis of etiologies and major symptoms [4].

Primary pain is induced by the disease process itself and may also be referred to as primary pain of central origin [3,4]. Patients may present with a general sense of discomfort or malaise, while experiencing unaccounted stabbing, painful, itching, aching, burning, or tingling sensations [4]. Secondary pain is more prevalent than primary pain, and arises from conditions that are brought on by PD [5]. There are multiple classifications of secondary pain, which include musculoskeletal (MSK) pain, radicular/neuropathic pain, dystonia-related pain, akathisia, and pain related to restless legs syndrome (RLS) [4]. MSK-related pain may arise due to problems of the muscles and bones in PD patients. Radicular and neuropathic pains are associated with tingling, cooling and numbing sensations. This is often a result of damage to the nerve or the nerve root- [6]. Dystonia-related pain is the most severe form of secondary pain, and often arises as a complication from dopaminergic therapies [4]. Patient experiencing a constant longing to move, and/or physical inability to remain still is a hallmark of akathisia. This is most commonly observed in the lower legs. Akathisia differs from RLS, which gives patients the urge to move while remaining in control of voluntary movements. Furthermore, unlike in akathisia, the pathophysiology of RLS is coupled to circadian rhythms [4].

Both pharmacological and non-pharmacological therapies may be used for the treatment and management of pain in PD patients [3]. Finding the most effective solution depends on the classification of the patient's pain. Although there are few studies of pain management in the PD population [4], clinical experience suggests that there are effective and safe pain management options in PD patients.

Pathophysiological basis for pain in PD

The pathophysiological mechanism involved in the presentation of pain among PD patients is not completely clear. However, the etiological basis of PD-related pain is multifactorial, with varying degrees of contribution from peripheral and central sources [7]. Pain in PD patients may manifest from the spino-hypothalamic tract [8]. These

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neurons project mainly to the hypothalamus, but have collaterals reaching the substantia nigra (SN), locus coeruleus, the striatum, amygdala and thalamus, carrying in this way nociceptive information to both the substantia nigra and striatum. Additionally, most of the pain afferent pathways end or relay information to the thalamus, particularly in the lateral and medial thalamic nuclei. The latter, mainly nucleus centromedian and lateral central nuclei, project and receive dense connections to and from the striatum.

Neurophysiological experiments have shown responses in neurons in the substantia nigra pars compacta (SNc) in both rodents and monkeys to noxious stimuli, suggesting a non-discriminatory role that was context dependent [9]. In addition, *in vivo* studies have suggested a functional segregation of the basal ganglia (BG) in the processing of pain [10].

Using PET and $H_2{}^{15}O$, Brefel-Courbon et al. [11] have observed that PD patients off medication have a reduced pain threshold and that this was associated with a greater activation of the pain matrix (insula, cingulate and prefrontal cortex). Levodopa reduces this abnormal cortical recruitment and increases pain threshold [12]. This suggests a role of the dopaminergic system in the modulation of pain. This finding that pain most frequently occurs in untreated patients or during "off" medication periods has also been found in other studies [13]. This suggests that pain coincides with low dopaminergic striatal activity. However, apomorphine does not modify the perception of pain, nor does it change the brain activation pattern when PD patients receive a painful stimulus [14]. As apomorphine is a pure dopaminergic agent whereas levodopa may also lead to an increase of noradrenaline release, it is possible that the modulation of pain may be more likely mediated by the noradrenergic system. It has also been suggested that PD patients are predisposed to painful sensations due to an abnormal nociceptive input processing in the central nervous system [15].

Functional outcomes of pain in PD

Despite being one of the more common non-motor symptoms of PD, pain remains largely understudied. Activities of daily living (ADL) that may diminish with pain in PD include standing, waking, labor and other common physical activities. Psychological and social well-being may also be compromised, as indicated in previous studies [16,17]. Indeed, both disability and depression have been shown to lower quality of life and worsen disease progression in patients with PD [17]. Taken together, these physical and psychological consequences of pain are referred to as the functional outcomes of pain in PD.

The trouble that these symptom combinations pose to PD patients combined with other hallmark motor symptoms of PD, necessitates that pain be more thoroughly studied within this patient population. Functional outcome encompasses the entire constellation of pain which may impact various aspects of life and includes both physical as well as psychological effects. Since these effects may vary from one patient to the next, the commonalities among patients with deficiencies in function should be studied. By measuring the effects of pain on ADL and functioning, we hope to fill-in this gap of our knowledge and ultimately improve the quality of life as well as the daily function of PD patients.

Material and methods

A neurologist conducted semi-structured interviews with 121 patients in 2011. Demographic results are summarized in Table 1. Out of 121 patients surveyed, 104 (86%) presented pain with PD. Patients were diagnosed with idiopathic PD and were regularly assessed for follow-up care at a community-based Parkinson's disease and movement disorders centre. Each session consisted of a 30-minute interview followed by a neurological assessment. The interviews covered two types of questions: ones related to the patient's experience with pain and ones related to the patient's ADL.

Patients were screened based on the presence or absence of experienced pain excluding headaches. A negative finding would end the interview and preclude any further questions. Follow-up questions further detailed the nature of the pain, its severity, location, frequency and duration. Patients reported whether

Table 1. Characteristics of patient population.

		Pain	No Pain	Total
Sex	Male	68	11	79
	Female	36	6	42
H&Y Stage	1	0	0	0
	2	41	9	50
	3	53	6	59
	4	9	2	11
	5	1	0	1
UPDRSIII	Median	27	23	26
Age	Mean ± SD	71.26 ± 11.22	72.65 ± 11.68	71.45 ± 11.25
Duration of PD	Mean ± SD	3.13 ± 2.92	3.59 ± 4.43	3.19 ± 3.15

UPDRS, Unified Parkinson's Disease Rating Scale

pain affected particular actions, such as standing, walking, labouring, and other common physical activities. Patients further reported the functional effects of their pain on the emotional and social levels. These effects were assessed through self-made questionnaires. The responses to these questions were compared to different parameters of pain symptom manifestations, such as the type, location and severity of pain. Factors relevant to functioning, but not directly related to pain, such as duration of PD, PD medication, and other comorbidities were analyzed to determine if they were confounding or if they produced functional deficits via an interaction with pain. Patients with a history of atypical parkinsonism, drug-induced parkinsonism or who suffered from external pain like major trauma, were excluded. The researchers also excluded patients with cognitive impairment to maintain the reliability of patients' accounts.

All patients were informed of the nature of the study and gave their written consent to participate. The local ethics review board approved the study.

Statistical analyses

All data analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). For the analyses of rates and proportions, Wald's chi-square test was used. Continuous data were expressed in terms of the mean and standard deviation. Bivariate relationships were assessed with Pearson's correlation coefficient. The relationship between pain in PD and clinical properties for the study groups were analyzed with multiple regression analysis. All p-values are two-tailed. P-values of <0.05 are considered statistically significant.

Results

Overall physical and emotional correlations

Various forms and locations of physical and emotional pain for 104 PD patients were recorded and used to analyze the presence or absence of correlations on ADL. Only groups large enough to make statistically significant conclusions will be highlighted in these findings, and some of the most notable findings are shown on Table 2. Of 104 patients, a significant number experienced dystonia in the upper limb ($p = 0.020$), paresthesia / neuropathy in the neck ($p = 0.021$) and musculoskeletal (MSK) problems in the upper limb ($p = 0.024$). Not surprisingly, PD-associated back problems and akathisia had a significantly negative correlation with patient mobility ($p = 0.004$ and $p = 0.002$, respectively). Akathisia has further been shown to negatively correlate with persistent turning in bed ($p = 0.014$) and exhaustion ($p = 0.009$).

The emotional and social consequences of pain in PD patients were also analyzed. Males are much more likely to report a decreased enjoyment of life than females in the presence of PD-associated pain ($p = 0.021$). In addition, back pain had a statistically significant negative correlation with social functioning ($p = 0.008$) and enjoyment of life ($p = 0.016$). Abdominal pain has been shown to have a positive correlation with the interference in one's hobbies ($p = 0.021$). The presence of akathisia is associated with diminished social functioning ($p = 0.001$), impaired emotional functioning ($p = 0.005$), and a decreased enjoyment of life ($p = 0.019$). Lastly, MSK issues have been negatively correlated with emotional health ($p = 0.026$).

Table 2. Correlations between pain and clinical variables through multiple regression analysis. Dependant variable: pains score.

		Pearson Corr	Sig.	N	Wald	Sig.	"OR (Exp(B))"	95% CI	
								Upper Bound	Lower Bound
Pain Scale	Emotional Functioning	0,26	0,02	76,00	4,82	0,03	2,35	1,10	5,03
	Sleep	0,34	0,01	58,00	5,85	0,02	3,15	1,24	7,98
	Enjoyment of Life	0,25	0,03	76,00	4,88	0,03	2,10	1,09	4,05
	Mobility	0,31	0,00	88,00	7,85	0,01	3,99	1,51	10,50
Back Pain	Social Functioning	0,28	0,01	88,00	6,83	0,01	3,96	1,41	11,12
	Emotional Functioning	0,17	0,11	88,00	5,73	0,02	3,13	1,23	7,95
	Mobility	0,33	0,00	88,00	5,10	0,02	3,88	1,20	12,56
	Exhaustion	0,31	0,01	69,00	5,70	0,02	10,07	1,51	67,12
Akathisic Pain	Social Functioning	0,35	0,00	88,00	4,33	0,04	3,42	1,07	10,88
	Enjoyment of Life	0,25	0,02	88,00	5,73	0,02	3,93	1,28	12,06
	Emotional Functioning	0,30	0,01	88,00	5,05	0,02	3,62	1,18	11,11
Musculoskeletal Pain	Exhaustion	0,05	0,71	69,00	5,33	0,02	19,97	1,57	253,88

Daily work, exhaustion, enjoyment of life and pain scale

PD duration has been shown as a positive predictive factor for observing problems with daily work ($p = 0.033$). Findings indicated that the likelihood of developing problems with daily work increased 1.25-fold with every additional year of working with PD. This effect is observed only when the age of diagnosis is kept constant. Hoehn and Yahr (H&Y) stage is a significant factor in predicting exhaustion due to pain ($p = 0.013$). With every increase in stage, the likelihood of exhaustion increased 5.45-fold. This effect occurred only when all other general demographic factors were taken into consideration. Being male with pain significantly reduced a person's enjoyment of life ($p = 0.010$). There is a 3.72-fold greater likelihood that males will report a diminished quality of life than females. Patients with a higher level of perceived pain experienced a 2.35-fold greater likelihood of having problems with emotional functioning ($p = 0.028$), a 3.15-fold greater likelihood of having troubles with sleep ($p = 0.016$), and a 2.10-fold greater chance of having a diminished quality of life ($p = 0.027$).

Locations and types of pain

The odds of developing mobility problems were shown to be 4-times greater for those with back pain than those without it ($p = 0.005$). The effects of neck, upper limb, lower limb and other areas on mobility limitations were statistically insignificant. The chance of developing social functioning problems was 4.00-fold greater for those with back pain than without it ($p = 0.009$). The effects of pain in the neck, upper limb, lower limb, and other areas were statistically insignificant for social functioning issues. Lastly, the odds of developing emotional functional problems were 3.13-fold greater for those with back pain than those without it. Indeed, pain in the neck, upper limb, lower limb and other areas were statistically insignificant with regards to emotional function.

The presence of akathisia increased the likelihood of mobility problems by 3.88-fold ($p = 0.024$), exhaustion by 10.0-fold ($p = 0.017$), social functioning problems by 3.42-fold ($p = 0.037$), lowered quality of life by 3.93-fold ($p = 0.017$) and diminished emotional function by 3.62-fold ($p = 0.025$). In addition, MSK pain has been shown to increase the likelihood of problems secondary to exhaustion by just under 20.0-fold ($p = 0.021$). The presence of paresthesia / neuropathy indicated a 4.65-fold greater likelihood of developing neck pain ($p = 0.024$), even when excluding the compounding effects of other types of pain. Upper limb pain can be significantly predicted by dystonia and MSK pain, while ignoring potential covariates ($p = 0.022$ and $p = 0.028$, respectively). However, when the covariates were introduced into the model and held constant, the effect disappeared.

Discussion

This is the first study to investigate the effects of pain on functional outcome in PD patients. Each patient was given a questionnaire to complete during his or her clinical visit. The answers to these questionnaires were reviewed and analyzed for statistical relationships (Table 2). Age of diagnosis, duration of PD, H&Y stage, UPDRSIII scale and sex showed statistically significant correlations to various measures of impairment in physical, social, and emotional well-being. Most notably, duration of PD was correlated to problems with daily work ($p = 0.033$); H&Y stage of PD at diagnosis was correlated to exhaustion ($p = 0.013$); and male gender was correlated to a lack of perceived enjoyment of life ($p = 0.010$). These findings suggest these factors are associated with a statistically significant negative impact on specific measures of functional outcome.

Logistic regression revealed a 125% increase in problems with daily work for each additional year with pain-associated PD symptoms ($p = 0.033$). Similarly, with every increase in H&Y stage of PD, the chance of exhaustion increased by 5.45-fold ($p = 0.013$). Thus, factors that exacerbate pain in patients with PD may negatively impact functional outcome. This is further supported by correlations with the level of pain on the pain scale, where 1 = little pain, 2 = moderate pain and 3 = high pain. Indeed, an increase in one interval on the pain scale was associated with a 2.0-fold increased likelihood of a diminished enjoyment of life ($p = 0.027$) and lack of emotional functioning (0.028), as well as a 3.0-fold increased likelihood of sleep impairment (0.016). Additional correlations were shown to be significant, however the study size of patients reporting those associations was too small to have adequate power. Thus, further studies with a larger population may reveal more significant trends.

Locations of pain, such as the neck, back, upper limbs and lower limbs were evaluated with respect to their effects on ADL. Back pain was correlated with poor social functioning (0.009), as well as impaired mobility (0.005). Surprisingly, back pain was not associated with diminished emotional functioning. Interestingly, differences in emotional functioning between populations with and without back pain were found to be significant, depression and anxiety being higher in the former [18]. In addition, there was a possible association between upper limb pain and certain problems in regular activities however the sample size was too small to test significance. These findings strongly suggest that the location of pain may influence the magnitude of the association between pain and functional deficiencies in ADL. Since back pain is the most debilitating and restricting form of pain measured, it is not surprising that it also had the most significant effects on ADL.

Patients presented with five major classes of pain: dystonic, neuropathic, akathisic, radicular, and musculoskeletal (MSK). Overall, akathisic pain was the most reliable predictor of negative effects on ADL. The presence of akathisic pain increased the likelihood of mobility problems by almost 4.0-fold ($p = 0.024$), exhaustion by 10.0-fold (0.017), social functioning problems by 3.5-fold (0.037), lack of enjoyment in life by approximately 4.0-fold (0.017) and problems in emotional functioning by 3.6-fold (0.025). In addition, MSK pain was significantly correlated with exhaustion (0.021). Under Pearson correlation, with other types of pain held constant, MSK pain increased the likelihood of exhaustion by almost 20.0-fold. Thus, it is evident that the effects of pain in PD on functional outcome vary depending on the class of pain. One possible explanation is that some forms of pain are more challenging to manage than others. Another possibility is that some forms of pain

may inherently be more debilitating or anxiety-provoking.

Overall, our results indicate that pain limits life in PD patients to a considerable extent. Unsurprisingly, back pain, MSK problems of the upper limb, and akathisia all negatively impact at least one dimension of ADL, social or emotional well-being. The deterioration of functioning due to associated pain extends to everyday activities such as cutting food, pill-taking, and simple housework. Correspondingly, tremor, rigidity, and bradykinesia have been shown to correlate strongly with a diminished quality of life (QoL) [19]. Our findings confirm the impact of mobility problems on QoL in PD, as presented in previous studies [20,21]. Both exhaustion and difficulty turning in bed are likely to contribute to falls, which in turn, influence ADL and QoL in PD patients. This is exacerbated by an increased incidence of injuries, time spent in a hospital [22], and the social stigma associated with falling in public. In addition, the fear of falling can prevent PD patients from taking part in activities, further restricting their ADL [23]. The ability to dress and undress oneself is a major indicator of a person's functional independence, and an inability to do so increases the patient's dependence on others. Simple interventions to facilitate everyday activities are therefore an important strategy for improving ADL. The contribution of fatigue to poorer QoL in PD had been previously noted, and has been rated among the most disabling symptoms of PD by a large percentage of patients [20,24].

Another important finding is the substantial decrease in enjoyment of life for male PD patients compared to female ones. Prevailing thought argues that women, in both healthy and PD populations, assimilate pain in a more intense and frequent manner than men [25,26], but our findings seem to suggest the opposite. It is interesting that male gender is correlated with a lack of perceived enjoyment in life, despite women being more likely to complain about painful signs and symptoms [27]. One explanation is that since males report pain less frequently, pain symptoms in males are more likely to remain unaddressed long enough to have a markedly large impact on quality of life. Identifying men with PD pain as a high-risk subgroup of patients seems warranted, since this subgroup may require different pain management intervention than women with the same magnitude of pain.

An important limitation of our study was that our approach in recruiting patients may have excluded severely affected PD patients with comorbidities. Notable strengths of our study include our evaluation of concomitant disorders, which may influence nociception. Furthermore, this analysis accounted for the effect of various localizations and types of pain. Finally, research with questionnaires filled out by PD patients and their caregivers may more accurately reflect feelings of pain in the life of PD patients.

Conclusion

Taken together, the determinants of pain-related functional outcome in Parkinson's patients include age and sex, as well as the presence or absence of back, MSK, and akathisic pain. Pain is considered to be one of the most underreported yet anxiety-provoking symptoms of PD, and one that disrupts many aspects of life. Knowing what factors predict the functional outcome of pain may assist clinicians in focusing their assessments and selecting treatment strategies to minimize the functional and emotional consequences of PD. Although there is a lack of effective treatments for painful symptoms, the results of this study demonstrate that pain should be actively diagnosed and that all parties should be informed and educated about its early management.

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Declaration of interest statement

The authors have no conflicts of interest to declare.

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