ORIGINAL ARTICLE

Relationship between pain and motor and non-motor symptoms in Parkinson's disease

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Background and purpose: Although female gender, depressive symptoms and medical conditions predisposing to pain are more common in patients with Parkinson's disease (PD) with pain, no study has yet explored the relationship between pain and other non-motor symptoms (NMS).

Methods: A total of 321 consecutive patients with PD [190 men/131 women aged 68.3 (SD 9.2) years] attending four Italian movement disorder clinics were studied. Demographic/clinical data were obtained by a standardized interview and the NMS scale. The association of pain with motor and NMS was assessed by multivariable logistic regression models.

Results: At the time of the study, 180 patients with PD (56%) reported chronic pain that, in most cases, was described as being muscular or arthralgic pain. Pain preceded the onset of motor signs in 36/180 patients. In the main-effect model, factors independently associated with pain were female sex [odds ratio (OR), 2.1; $P = 0.01$], medical conditions predisposing to pain (OR, 2.9; $P < 0.001$), Hoehn–Yahr staging (OR, 1.9; $P = 0.04$), motor complications (OR, 4.7; $P = 0.04$) and NMS belonging to the sleep/fatigue (OR, 1.6; $P = 0.04$) and mood/cognition (OR, 1.6; $P = 0.03$) domains. Most explanatory variables in the multivariable analysis were similarly distributed in patients in whom pain may have been related to PD or to a cause other than PD.

Conclusions: We confirm that pain in PD is more frequent in women and in subjects with medical conditions predisposing to painful symptoms. Moreover, this strengthens the association between pain and motor severity measures and NMS domains, particularly sleep and mood disturbances.

Introduction

Parkinson's disease (PD) is characterized by degeneration of several dopaminergic and non-dopaminergic brain areas and by a wide spectrum of motor and non-motor symptoms (NMS) including pain [1–5]. Muscular/arthralgic and dystonic pain are the most common pain types, with radicular and central neuropathic pain being reported less often [4,5]. The different pain types do not point to a clear relationship with PD motor abnormalities and respond in a variety of ways to dopaminergic medication [6]. This raises the possibility that non-motor/non-dopaminergic factors contribute to pain. Supporting this view, female gender, depressive symptoms and medical conditions predisposing to pain (diabetes mellitus, osteoporosis, rheumatic disease, degenerative joint disease, arthritis) seem to be more frequent in patients with PD with pain [4,7].

In PD, neurodegeneration in several cortical and subcortical structures may contribute to abnormalities in pain processing as well as to other NMS in

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addition to pain [8,9]. However, no study has yet explored the relationship between pain and the spectrum of NMS that may manifest themselves in PD. In this multicenter cross-sectional study, we therefore examined the association between pain and motor and non-motor factors in a large cohort of patients with PD.

Methods

Subjects

Patients enrolled consecutively at the movement disorder clinics of Bari, Rome, Venice and Verona from January to October 2015 participated in this multicenter cross-sectional observational study. The study was designed '*a priori*' to test the proposed target. Idiopathic PD was diagnosed according to published criteria [10]. Patients with cognitive disturbances (Mini-Mental State Examination score < 24) were excluded. Patients with PD gave their consent to participate in a study approved by the local ethics committee but were not informed of the study hypothesis.

Demographic and clinical information

A standardized interview collected patients' demographic/clinical data, including age, sex, age at PD onset, antiparkinsonian therapy [levodopa equivalent daily dose (LEDD) provided by dopamine agonists and catechol-ortho-methyltransferase / monoamine oxidase B inhibitors was calculated as reported] [11], modified Hoehn–Yahr (HY) staging (during the OFF state) [12] and information on any chronic pain that had been present at the time of the study for at least 3 months. Pain quality was classified as dystonic pain (pain associated with dystonic movements and postures), musculoskeletal pain (aching, cramping, arthralgic, joint), peripheral neuropathic pain (pain in the territory of a root or nerve) and central neuropathic pain (burning, tingling, pins and needles, or bizarre quality) [13,14]. According to previous reports [5], musculoskeletal pain was stratified as muscular pain (aching/cramping pain in muscles) and arthralgic pain (stiffness after rest and pain with motion, confined to joints). As headache and facial pain are characterized by a relatively well-known pathophysiology, we decided, similarly to previous studies on pain in PD, not to consider these conditions. The patients' opinion regarding the response of pain to antiparkinsonian medications was assessed by asking patients whether antiparkinsonian medication could abolish or consistently reduce (50% reduction or more on a visual analog scale) pain. If so, then PD-related pain was diagnosed [4]. We also checked for motor complications (fluctuations/dystonia/dyskinesia) and medical conditions predisposing to pain, i.e. diabetes mellitus, osteoporosis, rheumatic disease, degenerative joint disease, arthritis and disc herniation were diagnosed on the basis of patients' medical history, clinical examination and laboratory tests.

Non-motor symptoms were assessed according to the NMS scale (NMSS) [15], a validated tool in PD providing information on the presence, severity and year of onset of several NMS included in nine domains, i.e. cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function and miscellaneous. The miscellaneous domain refers to pain unexplained by known conditions, ability to taste or smell, weight changes and excessive sweating. As pain was assessed separately, the miscellaneous domain was excluded from the analysis. NMS had to occur for at least 3 months to be considered as present, even though the NMSS evaluated the burden only in the last month [15].

Statistical analysis

Data are expressed as mean ± SD (range), unless otherwise indicated, and analysed using the Stata 11.0 package (Stata Corporation, College Station, TX, USA). Crude differences across groups were evaluated by the chi-square test, Fisher's test, *t*-test and one-way ANOVA as appropriate. Logistic regression analysis (with pain as the outcome variable) evaluated the association between pain and the study variables. Odds ratios, two-sided 95% confidence intervals and *P*-values were computed. A backward multivariable logistic regression analysis was performed to yield a model containing the essential variables only (main-effects model), i.e. the variables that were independently associated with pain [16]. $P < 0.05$ was considered to be significant.

Results

Demographic and clinical features of the study population

Over the study period, 321 patients (190 men/131 women aged 68.3 ± 9.2 years; range, 33–86 years) met the eligibility criteria and participated in the study. The patients' mean age at motor symptom onset was 61.9 (SD 9.9; range 32–85) years, mean disease duration 6.6 (SD 4.8; range, 1–30) years and mean HY staging 1.9 (SD 0.6; range, 1–4). Motor

complications were present in 29 patients (9%). Twenty-eight patients with PD (8.7%) were not taking any medication, 103 (32.1%) were taking levodopa alone, 49 (15.3%) were taking dopamine agonists alone and 141 (43.9%) were taking multiple categories of drugs. The LEDD was 545 ± 377 (range, 0–2040) mg.

At the time of study, 180/321 patients with PD (56%) had been experiencing pain for at least 3 months. Dystonic pain was reported by 26/180 patients, muscular pain by 81/180 patients, arthralgic pain by 109/180 patients, peripheral neuropathic pain by 34/180 patients and central neuropathic pain by 4/180 patients. Forty-two patients reported more than one pain type. Pain was located in the neck (10%), shoulder (18%), arm (13%), back (26%) or leg/foot (33%). Pain before the onset of motor signs was reported by 36/180 patients (20%). Clinical and laboratory evidence of medical conditions predisposing participants to pain was found in 147 patients and included diabetes (n = 28), osteoporosis (n = 35), rheumatic disease (n = 3), degenerative joint disease (n = 51) and disc herniation (n = 45). Fifteen patients suffered from more than one disease. NMS were attributed to the cardiovascular domain in 95/321 patients (NMSS subscore, 1.2 ± 2.9), sleep/fatigue domain in 249/321 patients (NMSS subscore, 6.6 ± 7.9), mood/cognition domain in 162/321 patients (NMSS subscore, 4.3 ± 8.1), perceptual problems in 41/321 patients (NMSS subscore, 0.5 ± 1.7), attention memory in 134/321 patients (NMSS subscore, 2.5 ± 5.2), gastrointestinal domain in 184 patients (NMSS subscore, 3.8 ± 5.2), urinary domain in 205/321 patients (NMSS subscore, 0.6 ± 0.5) and sexual domain in 50 patients (NMSS subscore, 1.1 ± 3.6). Overall, 314/321 patients had NMS belonging to at least one of the study domains.

Univariable comparison of patients with and without pain

When we compared patients who had pain with patients who did not (Table 1), we found that women, medical conditions predisposing to pain, HY staging and motor complications were significantly more frequent/greater in the pain group. By contrast, age, age at PD onset, PD duration and LEDD were similar in the two groups.

Among NMS (Table 2), the cardiovascular, sleep/fatigue and urinary domains were more frequent in the pain group and were associated with higher NMSS scores; the mood/cognition and attention memory domains were more frequent in the pain group although scores were similar in the two groups; the gastrointestinal domain scores were higher in the pain group; and, lastly, the frequency and NMSS score of perceptual problems and sexual disturbances did not differ significantly in pain and non-pain groups.

Multivariable analysis

A first backward multivariable logistic regression analysis included age, female sex, medical conditions predisposing to pain, PD duration, referral, HY staging, motor complications and the number of patients reporting each NMS domain. The resulting main-effects model (Model 1, Table 3) indicated female sex, medical conditions predisposing to pain, HY staging, motor complications, sleep/fatigue and mood/cognition as significant explanatory variables.

A second backward multivariable logistic regression analysis was performed including the aforementioned demographic/clinical variables except number of patients reporting each NMS domain. The latter variable was substituted by NMSS scores from the various domains. The resulting main-effects model (Model 2, Table 3) included medical conditions predisposing to pain, HY staging, motor complications, sleep fatigue and mood/cognition domains as significant explanatory variables.

The final models did not retain the significant associations between pain and the cardiovascular, gastrointestinal and urinary domains that we

Table 1 Demographic and motor features of 321 patients with Parkinson's disease according to the presence of pain

	Patients with pain (n = 180)	Patients without pain (n = 141)	P
Female sex	90 (50)	41 (29)	<0.001
Mean age of motor sign onset (years)	62.4 ± 8.8 (32–83)	61.4 ± 11.1 (35–85)	0.29
Mean duration of motor signs (years)	6.4 ± 4.4 (5–30)	6.7 ± 5.2 (8–30)	0.33
No. of patients with medical conditions predisposing to pain	106 (59)	41 (30)	<0.001
Mean Hoehn–Yahr staging	2.02 ± 0.6 (1–4)	1.8 ± 0.5 (1–3)	0.03
No. of patients with motor complications	23 (13)	6 (4)	0.02
Mean levodopa equivalent daily dose (mg)	549 ± 377 (0–2040)	540 ± 377 (0–1960)	0.83

The data are given as n (%) or mean ± SD (range).

Table 2 Non-motor features of 321 patients with Parkinson's disease according to the presence of pain

Non-motor symptoms scale domains	Patients with pain (n = 180)	Patients without pain (n = 141)	P
No. of patients			
Cardiovascular domain	64 (35)	31 (22)	0.008
Sleep/fatigue domain	151 (84)	98 (69)	0.002
Mood/cognition	102 (57)	60 (42)	0.01
Perceptual problems	25 (14)	16 (11)	0.49
Attention/memory	84 (47)	50 (35)	0.04
Gastrointestinal	110 (61)	74 (52)	0.12
Urinary	125 (69)	80 (57)	0.02
Sexual function	27 (15)	23 (16)	0.75
Mean score			
Cardiovascular domain	1.55 ± 3.56 (0–24)	0.66 ± 1.76 (0–12)	0.003
Sleep/fatigue domain	7.64 ± 8.73 (0–48)	5.23 ± 6.36 (0–27)	0.003
Mood/cognition	4.75 ± 7.81 (0–54)	3.65 ± 8.27 (0–61)	0.11
Perceptual problems	0.44 ± 1.36 (0–10)	0.45 ± 1.43 (0–20)	0.52
Attention/memory	2.61 ± 5.01 (0–33)	2.37 ± 5.37 (0–32)	0.34
Gastrointestinal	4.22 ± 5.64 (0–28)	3.18 ± 4.57 (0–24)	0.04
Urinary	6.27 ± 7.79 (0–36)	4.81 ± 7.81 (0–36)	0.04
Sexual function	1.04 ± 3.70 (0–24)	1.04 ± 3.32 (0–24)	0.54

The data are given as n (%) or mean ± SD (range).

Table 3 Main-effects models

Patients with pain (n = 180) vs. patients with no pain (n = 141)	Odds ratio	95% confidence interval	P
Model 1			
Female sex	2.1	1.2–3.2	0.01
No. of patients with medical conditions predisposing to pain	2.9	1.8–4.8	<0.001
Hoehn–Yahr staging	1.9	1.1–3.7	0.04
No. of patients with motor complications	4.7	1.2–16.6	0.04
No. of patients reporting sleep/fatigue domain	1.6	1.1–2.8	0.04
No. of patients reporting mood/cognition domain	1.6	1.2–2.6	0.03
Model 2			
No. of patients with medical conditions predisposing to pain	2.7	1.3–5.4	0.002
Hoehn–Yahr staging	2.1	1.1–3.8	0.04
No. of patients with motor complications	4.1	1.1–21.2	0.04
Sleep/fatigue domain score	1.1	1.05–1.1	0.02
Mood/cognition domain score	1.1	1.05–1.2	0.04

observed upon univariable testing (Table 2). The analysis revealed that the association between pain and the cardiovascular domain was confounded by the sleep/fatigue domain and medical conditions potentially predisposing to pain; the association between pain and the gastrointestinal domain was confounded by the cardiovascular, sleep/fatigue and urinary domains; and the association between pain and the urinary domain was confounded by HY staging and the cardiovascular domain and sleep/fatigue domains.

Distribution of the explanatory variables in patients with pain

We identified three groups by stratifying the 180 patients with pain according to the patients' opinion regarding the response of any form of pain to antiparkinsonian medications and to the presence of medical conditions potentially predisposing to pain. The distinctive features of the three groups are shown in the footnote of Table 4. Most explanatory variables from the multivariable analysis were similarly distributed in the three groups (Table 4). Only motor complications were significantly more frequent in Group 1 (Table 4). The three groups also displayed differences in the quality of pain, i.e. muscular pain was significantly more common in Group 1, whereas arthralgic pain was more frequent in Group 2 (Table 4).

Discussion

In this study, the presence of pain in PD was independently associated with female sex, medical conditions predisposing to pain, HY staging, presence of motor complications and both the frequency and burden of NMS belonging to the sleep/fatigue and mood/cognition domains.

The higher rate of pain that we found in women is in keeping with previous reports [4–7] and with the

Table 4 Distribution of explanatory variables from multivariable analysis and quality of pain in three groups of patients

	Group 1 (n = 38)	Group 2 (n = 85)	Group 3 (n = 57)	P
Female sex	23 (60)	44 (52)	24 (42)	0.22
Mean Hoehn–Yahr staging	2.1 ± 0.5	2.1 ± 0.6	2 ± 0.6	0.37
No. of patients with motor complications	20 (53)	17 (20)	20 (35)	0.001
Sleep/fatigue domain				
No. of patients	31 (82)	75 (88)	47 (82)	0.51
Mean score	8.6 ± 8.8	6.9 ± 8.1	8.1 ± 9.4	0.54
Mood/cognition domain				
No. of patients	24 (63)	49 (58)	29 (51)	0.48
Mean score	4.6 ± 6.6	4.9 ± 8.8	4.4 ± 6.9	0.93
No. of patients with				
Dystonic pain	26 (68)	0	0	<0.0001
Muscular pain	22 (58)	29 (34)	30 (53)	0.03
Arthralgic pain	18 (47)	61 (72)	30 (53)	<0.0001
Peripheral neuropathic pain	6 (16)	21 (25)	7 (12)	0.15
Central neuropathic pain	0	1 (1.2)	3 (5)	0.16

Forty-two patients reported more than one type of pain. Group 1 included patients with a positive pain response to dopaminergic medication; Group 2 included patients with medical conditions predisposing to pain and pain that did not respond to dopaminergic medication; Group 3 included patients with no clinical or laboratory evidence of medical conditions predisposing to pain and no response to dopaminergic medication. The data are given as n (%) or mean ± SD.

widely reported observation that pain conditions are more common in women [17]. Likewise, the higher frequency of pain in patients with medical conditions predisposing to pain, the tendency of pain frequency to increase as parkinsonian motor signs progress [4–6] and the association of pain with mood symptoms [6,7] confirm previous findings. It is worth noting that most previous studies, unlike ours, did not consider the contribution of confounding factors, whereas our multivariable analysis showed that the aforementioned variables are independently associated with pain in PD.

The association that we detected between pain and sleep disturbances is a novel finding. However, the presence of restless leg syndrome in the sleep/fatigue domain of the NMSS might have biased our observation. Although, in some cases of restless leg syndrome, sensations can be referred to as painful, the NMSS specifically inquires as to urge and does not mention pain. Despite this limitation, the association that we observed between pain and both the sleep/fatigue and mood/cognition domains is likely to have pathophysiological implications. Although abnormalities in pain processing may arise from decreased basal ganglia dopamine levels [18], there is some evidence suggesting that changes in pain-processing mechanisms documented in PD might also reflect neurodegeneration in non-dopaminergic structures that mediate pain processing in the spinal cord, brainstem, diencephalon and limbic system [9]. As mechanisms underlying sleep/fatigue, restless leg and mood symptoms are believed to be related, at least in part, to brainstem structures and to neurotransmitters other than dopamine [9], the association that we observed in this study between pain and the aforementioned NMS domains might reflect the involvement of closely related brainstem regions in the pathological process and/or shared abnormalities in non-dopaminergic structures that contribute to both pain and certain NMS [18].

Although the cardiovascular, gastrointestinal and urinary domains of NMSS were associated with pain in the univariable analysis, multivariable models indicated that the associations were due to a confounding effect by variables related to PD motor severity and/or brainstem involvement.

There may be several reasons underlying the independent associations between pain and medical diseases potentially predisposing to pain. These diseases, as opposed to PD itself, might be responsible for pain in some patients. Alternatively, the contribution of several motor and non-motor factors may be needed for pain to develop in PD. In an attempt to shed light on this issue, we examined the distribution of explanatory variables from the multivariable analysis in three subgroups of patients with pain, i.e. patients who reported an improvement in pain after dopaminergic medication, patients with medical conditions predisposing to pain in whom pain did not respond to dopaminergic medication and patients with no clinical or laboratory evidence of medical conditions predisposing to pain in whom pain did not respond to dopaminergic medication. We observed a similar distribution of most variables across groups. The higher frequency of motor complications in patients with pain who responded to dopaminergic drugs is likely

to reflect the inclusion criteria. We therefore believe that the explanatory variables could contribute to pain in the three groups. Hence, the quality of pain in the three groups of patients with pain differed despite the similarities in the distribution of the explanatory variables. This would indicate that additional factors (such as postural abnormalities secondary to rigidity/bradikinesia, motor fluctuations and medical conditions predisposing to painful symptoms) are, as we previously suggested [9], superimposed on background abnormalities displayed by patients with PD both with and without pain, and contribute to the varying quality and site of pain [9].

This study has certain limitations. The sample that we recruited was characterized by a high proportion of patients staging <3 on the HY scale, a relatively short mean duration of follow-up and a low frequency of motor fluctuations. Therefore, information from our sample mainly refers to an early stage of PD. This may have contributed to the lack of association between pain and perceptual/cognitive domains. In this series, pain was present in 56% of the cases enrolled, a figure that is in keeping with data from previous studies [2,3]. The heterogeneous quality and body site of pain observed in our sample as well as the small number of patients experiencing pain before the onset of motor signs are also in accordance with previous reports [4,12,13,19]. Due to study power considerations, we could not evaluate whether pain and explanatory variables had different relationships in these subgroups of patients. For the same reason, we considered all of the medical conditions potentially predisposing to pain together and we did not therefore assess the role played by the presence and severity of each specific condition. Differential recall and misclassification of exposure status between patients with and without pain was unlikely because ascertainment was conducted by means of similar methodology in both groups. Our assessment of the relationships between pain and perceptive/cognitive problems was limited by the clinical characteristics of the study cohort and needs to be re-evaluated in patients over a longer follow-up period. The response of pain to dopaminergic medication was assessed by a visual analog scale because more specific pain scales were not available at the time of study [20]. Notwithstanding these observations, we feel confident that our study procedures excluded or minimized the major biases inherent to cross-sectional investigations and provided valid conclusions.

In conclusion, this study conducted on a sample of patients with mainly early PD shows that pain is more frequent in women and in subjects with medical conditions that predispose to painful symptoms. This study also strengthens the independent association between pain and measures of motor severity and reveals, for the first time, an independent association between pain and NMS domains, particularly sleep and mood disturbances.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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