Pain as a Nonmotor Symptom of Parkinson Disease

Evidence From a Case-Control Study

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Objective: To determine whether pain is more frequent among people with Parkinson disease (PD) than among age-matched controls.

Design: Case-control study

Patients and Methods: Logistic regression models taking into account type of pain, time between pain and PD onset, and possible confounders were used to compare 402 PD patients with 317 age-matched healthy control subjects.

Results: The overall frequency of pain was significantly greater in PD patients than in controls (281 [69.9%] vs 199 [62.8%]; $P=.04$), mainly because the healthy control group lacked dystonic pain. Conversely, the frequency of nondystonic pain was similar among PD patients and controls (267 [66.4%] vs 199 [62.8%]; $P=.28$). Nevertheless, we observed a significant association between PD and nondystonic pain, beginning after the onset of parkinsonian symptoms (odds ratio, 2.1; 95% confidence interval, 1.4-2.9). Cramping and central neuropathic pain were more frequent among PD patients than controls. About one-quarter of patients who experienced pain reported pain onset before starting antiparkinsonian therapy.

Conclusion: These data support the hypothesis that pain begins at clinical onset of PD or thereafter as a nonmotor feature of PD.

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P ATIENTS WITH PARKINSON DISease (PD) often complain of painful sensations that may involve body parts affected and unaffected by dystonia.[1-7] Pain in nondystonic body parts may have cramping and arthralgic features, as well as features of peripheral or central neuropathic pain.[1,6] The high frequency of these pain disorders in the general population makes it hard to establish whether pain is more frequent among people with PD than among age-matched controls. Although the 3 pertinent controlled studies (1 published in abstract form alone)[5-7] found a higher frequency of pain among PD patients than among controls, they provided inconclusive results, owing to limitations in study design. Most important, they failed to distinguish between dystonic and nondystonic pain, used as controls a relatively small group of participants with diseases who may not have fully represented the variable of interest in the source population, and did not take into account the time between pain and PD onset.[5,6] Finally, 2 of 3 studies focused on back pain alone.[5,6]

To clarify whether pain should be included among the nonmotor features of PD, we assessed the frequency of chronic pain in a large sample of PD patients and age-matched controls. In designing the study, we took into account the type of pain, the time between pain and PD onset, and possible confounding by relevant variables to ensure dependable results.

METHODS

Patients with PD were selected from consecutive outpatients attending the participating centers from November 1, 2006, to March 31, 2007. Idiopathic PD was diagnosed according to published criteria.[8] Patients with Mini-Mental State Examination scores of less than 24 were excluded. Healthy control subjects, recruited from relatives of outpatients attending the participating centers during the study period, were frequency-matched to case patients on 5-year age stratum, sex, and referral center. Case and control participants were asked to participate in a study on pain approved by the local ethics committee and were not informed of the study hypothesis.

Age, sex, age at PD onset, antiparkinsonian therapy, modified Hoehn-Yahr staging, Unified Parkinson Disease Rating Scale (UPDRS) part III (during the *on* state) and part IV motor scores, and information on any pain present at the time of study and lasting for at least 3 months were recorded by assessors who were unaware of the study hypothesis. In accordance with previous reports,[1-7] pain associated with visible dystonia was defined as dystonic pain, whereas nondystonic pain was classified as cramping (aching pain in muscles), arthralgic (stiffness after rest and pain with motion, confined to joints), peripheral neuropathic (pain in the territory of a root or nerve), and central neuropathic pain (burning, tingling, formication, or bizarre quality). Pain localization, age at pain onset, and severity on a visual analog scale were also recorded. Headache and other facial pain were not analyzed. Medical conditions associated with or predisposing participants to painful symptoms (ie, diabetes mellitus, osteoporosis, rheumatic disease, degenerative joint disease, arthritis, and disc herniation) were checked by direct clinical examination and clinical records. The Beck Depression Inventory was administered to assess depression. Finally, we determined whether pain developed before, at the same time as, or after the reference age. This was the age at first PD symptoms for case patients. The reference age for controls was obtained by subtracting the mean disease duration of case patients included in the corresponding age stratum from the age of the control.

Unless otherwise indicated, all values are expressed as mean (SD). Intraclass correlation coefficients, χ^2 tests, *t* tests, 1-way analysis of variance and Newman-Keuls post hoc tests, and logistic regression analysis were calculated using Stata statistical software, release 8 (StataCorp, College Station, Texas), where appropriate. $P<.05$ was considered to be significant. Study power was assessed using the Schlesselmann equation for unmatched studies with an unequal case-control ratio,[9] assuming a 2-fold increase in the risk of having PD (2-sided $\alpha=.05$).

RESULTS

TEST-RETEST STUDY

Repeatability of data on ages at pain and PD clinical onset was checked 6 months after the initial interview in a randomly recruited sample including 18 case and 22 control participants. These participants were similar to the overall sample with regard to demographic characteristics (data not shown). Both the case and control groups had high repeatability in recalling age at pain onset (>0.80)[10] (patients with PD: intraclass correlation coefficient, 0.99; $P<.001$; controls: 0.95; $P<.001$) and PD onset (intraclass correlation coefficient, 1.0; $P<.001$)

CASE-CONTROL STUDY

Participation rates were 98% among PD patients and 92% among healthy controls. Patients with PD (n=402) and controls (n=317) were similar with regard to age (67.4 [9.1] vs 65.5 [10.4] years; $P=.11$), sex (148 women [36.8%] vs 138 women [43.5%]; $P=.33$), and years of schooling (8 [4] vs 8.6 [4.3]; $P=.10$), but differed for the presence of depression (67 [16.7%] vs 19 [6.0%]; $P=.001$) and medical conditions associated with painful symptoms (99 [24.6%] vs 112 [35.3%]; $P=.02$).

Mean age of PD onset was 59.7 (9.9) years. The mean Hoehn-Yahr stage was 2.2 (0.8) (range, 1.5-5.0). The mean UPDRS part III score was 20.8 (10.2). Of 402 PD patients, 35 (8.7%) were receiving no medication, whereas 130 (32.3%) were taking levodopa alone, 61 (15.2%) dopamine agonists alone, and 176 (43.8%) both drugs. A total of 144 patients (35.8%) had dyskinesia (16 [4.0%]), motor fluctuations in parkinsonian disability (42 [10.4%]), or both (86 [21.4%]). Dystonia was present in 68 patients (16.9%), of whom 30 (7.5%) also had dyskinesia. The UPDRS part IV score was 2.2 (3.0).

At study time, more PD patients than controls reported experiencing pain for at least 3 months (281 [69.9%] vs 199 [62.8%]; $P=.04$). Pain associated with visible dystonia was more frequent among PD patients than controls (27 [6.7%] vs 0; $P<.001$). In PD patients, mean dystonic pain onset was at age 64 (7) years, and the age at onset of parkinsonian symptoms was 60 (9) years ($P=.04$). Dystonic pain was localized in the neck or shoulder (9 [2.2%]), arm (4 [1.0%]), and leg or foot (22 [5.5%]), and the mean severity on the visual analog scale was 6 (2).

Nondystonic pain was reported with comparable frequency by case and control subjects (267 [66.4%] vs 199 [62.8%]; $P=.28$); 15 PD patients reported having both dystonic and nondystonic pain. Mean age at onset of nondystonic pain was 60.2 [12.0] years in PD patients and 54.9 [13.4] years in controls ($P<.001$). Both cases and controls reported the onset of nondystonic pain either several years before the reference age (PD patients, 11 [3] years from pain onset to PD clinical onset) or at/after the reference age (**Table**). Considering individuals without pain as the reference category, and stratifying by pain arising before or at/after the reference age, a multivariable logistic regression model (taking into account age, sex, referral center, years of schooling, depression, and medical conditions associated with painful symptoms) yielded a significant association of PD with nondystonic pain arising at the reference age or thereafter (Table). The subsequent analysis therefore focused on nondystonic pain starting at or after the reference age.

Cramping and central neuropathic pain were significantly associated with PD, whereas arthralgic and peripheral neuropathic pain were not (Table). The study power was more than 80% for arthralgic pain and less than 80% for peripheral neuropathic pain. The shoulder, back, and leg were more frequently affected among PD patients than controls (Table), even after adjusting for pain types that were not associated with PD, ie, arthralgic and neuropathic pain (data not shown). Neck and arm pain yielded no significant association with PD, but the study power was less than 80%. Cases and controls had comparable severity of nondystonic pain on the visual analog scale (5.5 [2.1] vs 5.6 [2.3]; $P=.30$). Similar nonsignificant findings were obtained for cramping, arthralgic, and peripheral and central neuropathic pain (data not shown).

Stratifying PD patients by dystonic pain (27 [6.7%]), nondystonic pain (170 [42.3%]), and no pain (205 [51%]) beginning at or after the onset of parkinsonian symptoms yielded similar age (69.7 [7] vs 67.7 [8.6] vs 66.7 [9.9] years; $P=.30$ on the post hoc test), sex (11 [2.7%] vs 74 [18.4%] vs 74 [18.4%] women; $P=.23$), years of schooling (7.7 [3.5] vs 7.7 [4.0] vs 8.5 [3.9]; $P=.15$ on the post hoc test), and disease duration (9.0 [8.0] vs

Table. Frequency and Distribution of Nondystonic Pain

	Patients With PD[a] (n=402)	Controls[a] (n=317)	OR[b] (95% CI)	P Value
No pain	134 (33.3)	118 (37.2)	1 [Reference]	. . .
Pain onset before the reference age	83 (20.6)	94 (29.7)	0.96 (0.6-1.5)	.84
Pain onset at/after the reference age	185 (46.0)	105 (33.1)	2.1 (1.4-2.9)	<.001
Type of Pain				
Arthralgic	102 (25.4)	67 (21.1)	1.1 (0.8-1.7)	.50
Cramping	46 (11.4)	17 (5.4)	2.5 (1.6-4.6)	.005
Peripheral neuropathic	19 (4.7)	11 (3.5)	1.3 (0.6-3.0)	.54
Central neuropathic	18 (4.5)	5 (1.6)	2.9 (1.1-8.4)	.04
Location of Pain				
Neck	25 (6.2)	15 (4.7)	1.1 (0.5-2.3)	.75
Shoulder	44 (10.9)	18 (5.7)	2.8 (1.4-5.8)	.004
Arm	31 (7.7)	16 (5.0)	1.7 (0.9-3.8)	.08
Back	63 (15.7)	38 (12.0)	1.9 (1.1-3.4)	.02
Leg or foot	80 (19.9)	45 (14.2)	1.9 (1.1-2.9)	.03

Abbreviations: CI, confidence interval; ellipses, not applicable; OR, odds ratio; PD, Parkinson disease.
[a] Data are given as the number (percentage) of participants.
[b] Adjusted for age, sex, referral center, years of schooling, depression, and medical conditions associated with painful symptoms.

7.7 [9.1] vs 7.4 [10.2] years; $P = .25$ on the post hoc test), whereas Hoehn-Yahr stage (2.7 [0.7] vs 2.2 [0.8] vs 2.1 [0.7]), UPDRS part III scores (28 [11] vs 21 [11] vs 20 [9]) and part IV scores (4 [3] vs 2 [3] vs 2 [3]), and levodopa daily dose (615 [363] vs 458 [373] vs 437 [352] mg) were significantly higher among patients with dystonic pain ($P < .05$ on the post hoc test). About one-quarter of patients with either dystonic pain (6/27 [22%]) or nondystonic pain (47/185 [25%]) reported the onset of pain before starting antiparkinsonian therapy.

Although our study did not specifically focus on the effect of anti-Parkinson medications on pain, patients reported that dystonia improvement secondary to changes in levodopa dosage resulted in decreased dystonic pain. Cramping pain was reduced, but never eliminated, by anti-Parkinson medications in some patients, whereas others did not report any benefit. Finally, patients reported no obvious relationship between levodopa-related changes in parkinsonian disability and neuropathic pain.

COMMENT

Our findings suggest that pain among PD patients is heterogeneous in quality, body localization, and relationship with the clinical onset of PD. In our sample, the overall frequency of pain was significantly greater among cases than controls, mainly because the healthy control group lacked dystonic pain. Conversely, the frequency of nondystonic pain was similar in PD patients and controls. Nevertheless, our analysis showed a significant independent association between PD and nondystonic pain starting at or after the onset of parkinsonian symptoms. With reference to such pain, cramping and central neuropathic pain subtypes were significantly associated with PD, whereas arthralgic and peripheral neuropathic pain were not; PD patients reported shoulder, back, and leg nondystonic pain more frequently than did controls.

The strict methods used in our case-control study minimized the major biases inherent to such investigations. Re-cruiting consecutive PD patients in a multicenter setting gave a series resembling the general population, including the high frequency of depression. Although the overall frequency of pain and the distribution of pain subtypes were comparable to those in previous series, as a service-based study, our survey probably overestimated the frequency of pain. Controls were not selected according to the variable of interest, and participants always remained unaware of the study hypothesis. Controls could have been less motivated than PD patients to recall their age at pain onset. However, the high reproducibility found for information on age at pain and PD onset among cases and controls minimized the possibility of differential misclassification. A bias owing to the assessors being unblinded to the case-control status was also unlikely because assessors were unaware of study hypotheses. Classifying complaints of nondystonic pain into distinct subtypes based on the patient's interview could have been unreliable. Nevertheless, this misclassification is unlikely to have affected the validity of our data on nondystonic pain overall because we differentiated nondystonic from dystonic pain on the lack of dystonic contractions in the body part affected by pain on clinical examination. Finally, when analyzing the results we adjusted for major possible confounders, such as age, sex, referral center, years of schooling, other medical diseases, and depression. These observations notwithstanding, we feel confident that our study procedures excluded or minimized the major biases inherent to retrospective case-control investigations and provided valid conclusions. Unsatisfactory study power might nevertheless have been responsible for the lack of association with pain localized in the neck or arm and with peripheral neuropathic pain. A larger study may be needed before definitive conclusions can be drawn about these issues.

Although some smaller studies found that drug-naïve patients with PD rarely complained of pain,[1,4] ours and other large studies[3,6] found that a consistent proportion of patients reported experiencing pain when they were drug-free.[3,6] This supports a link between pain and patho-

physiological PD mechanisms. Because basal ganglia are involved not only in motor functions but also in the processing of nociceptive and non-nociceptive inputs, it is conceivable that a nigrostriatal damage leading to a dysfunction of the control exerted by basal ganglia on cerebral areas devoted to processing nociceptive inputs might at least partly account for the increased risk of pain in PD.[11] Recent findings show that PD patients both with and without pain may have a low heat pain threshold (regardless of being in an *on* or *off* state), and abnormal pain-evoked responses suggest that PD patients may be predisposed to developing pain.[12,13] Additional mechanisms other than dopamine might contribute to such a predisposition, as suggested by the apparently poor response of nondystonic pain to levodopa reported by our patients. Because our design did not allow an in-depth evaluation of the effect of anti-Parkinson therapy on pain, an ad hoc study would be necessary to clarify the issue. The heterogeneous pain presentation may be at least partly determined by locoregional factors. In accordance with this hypothesis, in our sample, most PD patients had pain in body regions where rigidity or bradykinesia is usually more marked, ie, the shoulders, back, and lower limbs. Although primary dystonia is usually not associated with pain (apart from cervical dystonia),[14] dystonic contractions might trigger pain in predisposed subjects. The differences in levodopa dosage and severity of PD and motor complications actually found among patients with dystonic and nondystonic pain might favor this clinical differentiation of pain. Owing to the cross-sectional approach, however, we could not validly assess whether and how the development of different pain types was really influenced by the above variables.

CONCLUSIONS

The results of this large case-control study supported by a representative case population and an appropriately matched control population suggest that dystonic or nondystonic pain beginning when PD has its clinical onset or thereafter should be considered a nonmotor feature of PD. The findings of this study may have implications for designing studies aimed at understanding pain mechanisms in PD and identifying specific treatment strategies.

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