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Prevalence of pain and depression and their coexistence in patients with early stage of Parkinson's disease

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Abstract

Depression and pain are common and often early non-motor symptoms of Parkinson disease (PD). The relationship between pain and depression in PD has been unsettled, with conflicting findings. The PD patients followed up at the general neurology outpatient clinics were requested to complete Beck Depression Inventory (BDI) and McGill pain questionnaire. The patients were categorized in three groups according to the Hoehn-Yahr (H-Y) stage of PD; mild (stage I&II), moderate (stage III) and advanced stage (stage IV&V), and group comparisons were performed in each group between those with and without pain. A total of 186 patients completed the questionnaires. Their mean age was 74±9.3 years, and the mean H-Y stage was 2.8±0.8.Sixty-nine percent of the patients reported pain symptoms of various natures. The BDI scores were significantly higher in the pain group ($P< 0.0001$) despite the absence of statistically significant differences in the mean age, H-Y stage, and duration of illness. Only PD patients of mild stage revealed significant difference of BDI scores between those with pain and without pain ($P <0.001$). Our results showed that pain is a common symptom in patients with PD and suggest that it may be related to depression in the early stage of the disease.

INTRODUCTION

Pain is a common symptom among individuals with Parkinson disease (PD) and is rated by patients as one of the most troublesome symptoms in both the early and advanced stages of PD.[1,2] Pain often precedes the motor symptoms by several years, and responds poorly to dopaminergic treatment.[3-8] Depression is, on the other hand, the most common neuropsychiatric disturbance of PD. It may occur early and may even precede the motor manifestation of PD.[9-16]It is not related to age or duration of illness.[17] In a community-based study, the prevalence of depressive symptomatology in PD patients was six times that of healthy age- and gender-matched controls.[10]

Although both pain and depression are common and often early non-motor symptoms of PD, there has been controversy regarding to the relationship between them. Several studies have reported that pain and depression are significantly inter-related in PD[2,18,19], while other reports have denied such a relationship, suggesting that pain and depression are independent conditions.[20-22] The reasons for such a discrepancy among studies are unclear, but may reflect the heterogeneity of the PD patients targeted in these studies, and differences in the methods employed.

In this study, we aimed to evaluate whether pain is associated with depression in patients with PD, for different Hoehn-Yahr stages at the outpatient clinic of community-based hospitals.

METHODS

A total of 186 consecutive patients with idiopathic PD according to the UK Parkinson Disease Brain Bank criteria, were recruited during a 1-year period from outpatient neurology clinics of three municipal hospitals in Nagano prefecture, located in the central part of Japan's main island. Their mean age was 74±9.3 years, and the mean Hoehn-Yahr stage was 2.8±0.8 (stage I&II, n=63; stage III, n=104; stage IV&V, n=19).

All the patients underwent MRI study of the brain before the diagnosis, and all responded to L-dopa. The eligible patients who consented to participate in this study had regular monthly or

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bimonthly visits to the outpatient clinic, and were continuously followed up there for the PD. Patients being treated for orthopedic or rheumatologic diseases such as rheumatoid arthritis and osteoarthritis were excluded. Patients complaining of back pain were included in the study, unless etiologies of pain were not apparent. All of the patients signed and completed the questionnaire by themselves.

Eligible patients completed the Beck Depression Inventory (BDI, Japanese version) for the evaluation of their depressive symptoms. The BDI is a self-rating scale, and its utility as a screening instrument for depression in PD has been established.[23,24] They were then asked if they commonly experienced pain in their daily lives, and if they answered in the affirmative, they were further asked to complete the McGill Pain questionnaire (Japanese version, short form) to characterize their pain. We used IRLSSG criteria, including the urge to move the legs to screen for restless leg syndrome (RLS). The absence or presence of motor fluctuations, dyskinesia, dystonia and tremor were ascertained by clinical charts and inquiries to the patients in the questionnaires. The patients were also asked to indicate the location of pain on a prepared printed body schema, and the presence or absence of temporal relationship between the occurrence or disappearance of pain and PD medication.

For the data analysis, we performed group comparisons after classifying the patients into three groups according to their Hoehn-Yahr stage of PD: mild (stages I&II), moderate (stage III) and advanced stage (stages IV&V). Group comparisons were also done between the patients with and without pain, using Student's t-test and Chi square test. We also compared the daily dose of L-dopa, the presence of wearing off, the presence of tremor and/or dyskinesia, and the use of analgesics between PD patients with and without pain.

Pain threshold study

A pain threshold examination of 20 consecutive PD patients with pain (mean age 74.5±10.7 years; five males and 15 females; 17 patients with stage III and three patients with stage IV) was performed by the two authors (K.A. and R.H.). Both C fibers and Aδ fibers were stimulated using a novel electrical stimulator (Pain Vision®, Nipro, Osaka, Japan). A gradually increasing pulsed current (frequency 50Hz, pulse width 0.3 ms) was applied to eight sites (both sides of the dorsum of hands, the medial forearms, the medial upper arms, and the dorsum of feet). The patients were asked to push a button when they first felt the electrical stimulation to be faintly painful, and we defined this current value as the threshold value. If this value was less than the mean value minus one standard deviation (SD) of age-matched controls, the patients were considered to have a lower pain threshold compared to the controls.[25]

RESULTS

Demographic profiles and clinical features of PD patients with and without pain

As shown in Table 1, in a total of 186 patients, 129 patients (69%) reported pain symptoms of various natures. No patients had off period dystonia or restless leg syndromes. The BDI scores were obtained from 178 out of the 186 patients; 8 patients returned the inquiry unanswered for unidentified reasons. In these 178 patients, the BDI scores of the 127 patients with pain were significantly higher than those of the 51 patients without pain (with pain 18.5±9.7, without pain 12.0±9.7 $p<0.0001$). The PD patients who reported experiencing the wearing off had significantly more pain than those without ($p<0.004$). However, 76% of the patients reported no temporal association between the pain and the individual doses of L-dopa.

There were no significant differences between pain and no-pain groups in terms of age, gender ratio, Hoehn-Yahr stage, presence or absence of resting tremor and/or dyskinesia, L-dopa dosage, or duration of the illness (Table 1).

The relationship between BDI score and Hoehn-Yahr stage in PD patients with and without pain

There was overall a positive correlation between BDI score and the progression of PD as indicated by Hoehn-Yahr stages (Figure 1). Among the mild-stage PD patients (Hoehn-Yahr stages I&II), the BDI scores of those with pain were significantly higher than the BDI scores of those without pain (with pain 6.6±7.9 without pain 5.4±6.7 $p<0.001$). However, in the patients with more advanced stages (Hoehn-Yahr stages III and IV&V), there was no such significant difference.

Characteristics of the pain

Throbbing, cramping, dull/soreness, shooting pain and tiring pain were the top five items described

Table 1: Demographic profiles and clinical features of the PD patients with and without pain.
129 patients reported pain, and 127 of these completed BDI, while 57 patients did not report any pain, 51 of these completed BDI.

	With pain (n=129)	Without pain (n=57)	p
Mean age	74.3 ± 9.0	74.3 ± 10.0	0.98*
M/F	55/74	25/32	0.86**
Yahr stage	2.7 ± 0.8	2.8 ± 0.8	0.485*
Duration of the illness (year)	8.3 ± 5.0	7.5 ± 4.4	0.268*
L-dopa (mg/day)	338.8 ± 110.0	330.7 ± 128.8	0.66*
BDI score ⩾ 10	18.5 ± 9.7[§] 27 (46%)	12.0 ± 9.7[§§] (79%)	**<0.0001***
Wearing off (%)	67/129 (48.1)	16/57 (28.1)	**0.004****
Dyskinesia (%)	23/129 (17.8)	10/57 (10)	>0.999**
Resting tremor (%)	80/129 (62%)	31/57 (17.5)	0.41**
Analgesic use	24/129	4/57	0.07**
Minor tranqulizer	8/129	3/57	>0.999**

* Student t-test, ** chi-square test
[§,§§]127 of 129 patients with pain and 52 of 57 patients without pain responded to BDI.

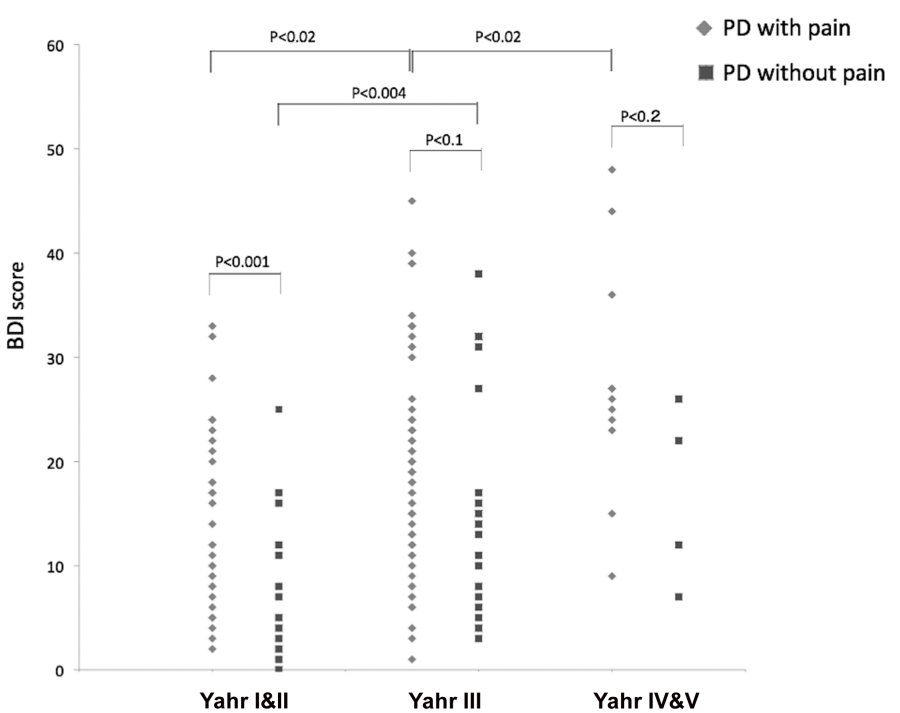

Figure 1. BDI scores and Hoehn-Yahr PD stages of the patients with and without pain.
In the mild-stage PD patients, there was significant difference of BDI score between those with pain and without pain (p< 0.001). There was a positive correlation between BDI score and the progression of PD as indicated by Hoehn-Yahr stages.

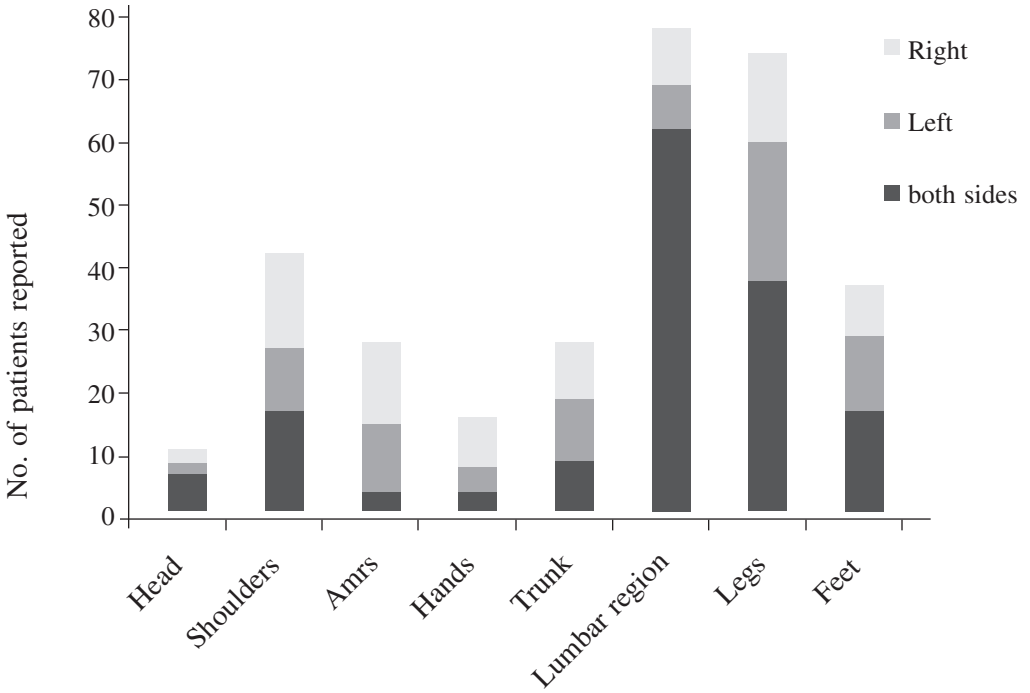

Figure 2. Topography of pain. The patients reported that their pain is most often felt in the lower extremities, and often bilaterally

on the McGill pain questionnaire by the patients with pain. The questionnaire revealed that 58% of the PD patients reported more than one type of pain. None of our patients reported the dystonic type of pain or painful RLS. Only 18.7% of the PD patients who reported pain used conventional nonsteroidal anti-inflammatory medications (NSAIDs) and no other analgesics.

Topography of pain

As shown in Figure 2, the patients reported that their pain was most often felt in the lower extremities, and often bilaterally.

Pain threshold

Among all body sites investigated in the pain threshold examination, we found that 17 of the 20 patients (85%) had at least one lower pain threshold site compared to the value obtained from control subjects. Nine of these 17 patients (53%) had a lower pain threshold on the same side as the initial motor disturbance; five patients (29%) had a lower pain threshold on the other side, and three patients (19%) showed a lower pain threshold on both sides although they had experienced pain on only one side.

DISCUSSION

Prevalence of pain and its characteristics in PD

In the present study, based on a self-answered questionnaire, 69% of 186 PD patients (mean Hoehn-Yahr stage 2.8) regularly seen at neurology outpatient clinics of community hospitals reported experiencing chronic pain, which was in line with previous studies reporting that pain is one of the most common non-motor symptom in PD, ranging from 11% to 83%.[2]

The characteristics of the pain reported by our patients were varied. They included throbbing, cramping, dullness/soreness, shooting and tiring pain in that order of frequency. In addition, 58% of the patients with pain had more than two pain types on the McGill questionnaire. These varied descriptions of pain and the tendency of suffering from more than two types of pain in a single patient are consistent with previous reports.[26]

The topography of pain reported by our patients showed that the lumbar region and the legs were the most frequent sites, followed by shoulder and arms, and that the pain was often experienced on both sides. These were consistent with the previous studies, reflecting the regions

where rigidity or bradykinesia is usually more marked.[27,28] Shoulder pain (or frozen shoulder), another well-known manifestation, often occurs as a presenting feature of PD.[6,29] The physiological mechanisms underlying pain in Parkinson's disease are unclear and may be diverse depending on the type of pain, or on the central or peripheral nociceptive pathways involved.[6,30,31] In an analysis of 106 PD patients with/or without pain, Zambito Marsala *et al*. reported that the pain threshold and pain tolerance were significantly lower in PD patients than in control subjects, and that there were significant inverse correlations of the pain threshold with motor symptom severity and BDI score.[32] Similar results have also been reported from other studies.[33-36] In the present study, we examined the pain threshold in 20 consecutive PD patients with pain using a novel electrical stimulator. We found that their pain threshold was decreased to less than the mean value minus 1SD of controls, which was consistent with previous studies. Although our present investigation was preliminary with a small number of patients studied, the results suggest that a decrease in the pain threshold may have been responsible for enhanced pain perception in certain PD patients in this population.

The relationship between pain and depression in PD

In the present study, 46% of the patients without pain and 79 % of those with pain were screened positive for depression by the BDI, clearly indicating that the presence of pain is significantly associated with higher BDI score ($p< 0.0001$) (Table 1). Regardless of presence or absence of pain, BDI scores and Hoehn-Yahr stages were significantly related to each other (Figure 1). However, group comparison revealed that it was at an early stage of PD that the presence of pain and BDI scores were most strongly related to each other ($p<0.001$) (Figure 1).

In previous studies, an increase in intensity of pain with the progression of PD was reported.[32,37,38] Comorbidity of depression and pain with possible common underlying biological pathways has been suggested.[39,40] Therefore, one might consider that the relationship between pain and depression could be most significant in the advanced stages of PD, which was not the case in the present study; only PD patients of Hoehn-Yahr stages I & II revealed significant difference of BDI scores between those with pain and without pain. The reason for this unexpected result is unclear. One explanation would be that the lesser amount of motor and/or non-motor complications in the early stage of PD, compared to those in later stages, may have made the association between pain and depression more apparent. In this regard, it should be noted that previous studies suggested that dystonic pain may account for the increased prevalence of pain among PD patients compared to age-matched populations.[21,27] Defazio *et al*. reported that PD patients with higher levodopa daily doses tended to show a significantly higher incidence of dystonic pain.[27] Thus, the absence of dystonic pain in our study may have reflected, unlike the previous studies, the relatively low average L-dopa dose used in our patient cohort. However, we could not rule out the possibility that this type of pain may have been under control in our patients with the adjustment of the L-dopa dose.

There has been controversy with regard to the inter-relationship between pain and depression in PD. Goetz *et al*. using the BDI, reported that severe depression was more common in PD patients experiencing pain.[18] In a community-based study, Ehrt *et al*. reported that 67% of 227 patients with PD suffered from pain, and there was a significant relationship between pain and depression as assessed by the Montgomery- Asberg Depression Rating Scales (MADRS) and the BDI.[19] On the other hand, Tinnazzi *et al*. and Hanagasi *et al*. reported the lack of association between pain and BDI scores in PD.[21,22] There was also report of significant inverse correlations of pain threshold and pain tolerance with motor symptom severity and Beck depression inventory.[32]

In conclusion, the results of the present study are in support of the previous studies that pain and depression are significantly inter-related, and that it is in the early motor stage of PD when their association is most evident. These results seem consistent with the view that both pain and depression in the early stage of PD may have common biological underlying mechanisms. However, it is also conceivable that unexplained pain in a patient's own perception may provoke secondary anxiety and/or depression. Could presence of pain predict concomitant or subsequent depression, or vice versa? Further longitudinal study on the patients with the early stage of Parkinson's disease is necessary to clarify this point.

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DISCLOSURE

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