Journal of the Neurological Sciences 392 (2018) 3–7

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Peripheral neuropathic pain in idiopathic Parkinson's disease: Prevalence and impact on quality of life; a case controlled study

Joy K. Adewusi[a], Marios Hadjivassiliou[b], Ana Vinagre-Aragón[b], Karen Ruth O'Connor[b,c], Aijaz Khan[b], Richard Adam Grünewald[b], Panagiotis Zis[b,*]

[a] Sheffield Institute for Translational Neuroscience, University of Sheffield, UK
[b] Academic Department of Neurosciences, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[c] Sheffield Health and Social Care NHS Foundation Trust, Sheffield, UK

ARTICLE INFO

Keywords:
Idiopathic Parkinson's disease
Pain
Non-motor symptoms
Peripheral neuropathy
Quality of life

ABSTRACT

Background and purpose: Pain is a frequent and debilitating non-motor symptom of Idiopathic Parkinson's Disease (IPD). The present study investigated the prevalence of pain and specifically peripheral neuropathic pain (PNP) in IPD, and ascertained any impact of PNP on quality of life (QoL).

Methods: Patients with IPD and age- and gender-matched controls were screened for overall pain using the King's Parkinson's Pain Scale (KPPS). PNP was assessed using the Michigan Neuropathy Screening Instrument (MNSI). QoL was assessed using the 36-Item Short Form Survey (SF-36).

Results: Fifty-one patients and 51 age and gender matched controls were recruited. The prevalence of overall pain was similar in the two groups (88.2% versus 94.1%, $p = 0.487$). However, patients with IPD had higher KPPS scores in fluctuation-related (4.9 ± 6.9 vs 1.1 ± 2.6, $p < 0.001$), nocturnal (6.6 ± 7.5 vs 1.7 ± 4.2, $p < 0.001$) and oro-facial (0.6 ± 2.0 vs 0.0 ± 0.0, $p = 0.040$) domains compared to controls.

Patients with IPD experienced more PNP compared to healthy control subjects (35.3% versus 13.7%, $p = 0.011$).

After adjusting for age, gender, disease duration and overall KPSS score, PNP correlated negatively with physical functioning score (beta −0.290, $p = 0.036$), emotional role limitations score (beta −0.319, $p = 0.032$) and general health perception score (beta −0.342, $p = 0.014$) domains of SF-36.

Conclusion: Peripheral neuropathic pain is prevalent in IPD and has a significant impact on QoL. The presence of burning pain is suggestive of small fibre neuropathy, but this symptom is not featured in KPSS and, therefore, a revision of the KPSS should be considered.

1. Introduction

Pain is a common and debilitating non-motor symptom (NMS) in Parkinson's disease (PD). The range of pain syndromes can be classified based on cause, origin, location, and chronicity. Examples of pain in PD include musculoskeletal, fluctuation-related pain and nocturnal pain [1].

Peripheral sensory neuropathic symptoms are frequently reported NMS in PD [2]. These include symptoms such as tingling, numbness, and peripheral neuropathic pain [3]. Indeed, large fibre peripheral neuropathy (PN) and small fibre neuropathy (SFN) are more prevalent in PD in comparison to the general population [4]. The exact mechanism of the pathogenesis of PN and SFN remains unclear [4]. Many studies have shown that in most PD cases PN is associated with abnormalities in vitamin B12, methylmalonic acid and/or homocysteine levels. Such abnormalities can occur as a result of malabsorption and it has been hypothesised that levodopa treatment might affect the vitamin absorption [5]. However, in other studies deposition of phosphorylated α-synuclein in cutaneous nerve fibers has been demonstrated, suggesting that the development of PN might be part of PD itself [6].

Pain related to SFN is commonly described as an unpleasant burning sensation predominantly affecting the feet and extending proximally as the disease progresses. Less commonly SFN can present with an asymmetrical distribution of the symptoms [7, 8]. This often occurs when the predominant pathology is affecting the sensory ganglia [9]. However, in both cases as the SFN progresses a global loss of intraepidermal nerve fibers will occur [7].

* Corresponding author at: Academic Directorate of Neurosciences, Sheffield Teaching Hospitals NHS Trust, Royal Hallamshire Hospital Glossop Rd, Sheffield, South Yorkshire S10 2JF, UK.
E-mail address: takiszis@gmail.com (P. Zis).

https://doi.org/10.1016/j.jns.2018.06.022
Received 14 March 2018; Received in revised form 22 June 2018; Accepted 24 June 2018
Available online 25 June 2018
0022-510X/

Peripheral neuropathic pain can be spontaneous (independent of any stimulus) or evoked by a noxious or non-noxious stimuli, as in hyperalgesia and allodynia, respectively [10, 11]. These neuropathic painful symptoms may cause considerable burden to patients, comparable to the motor burden of the disease [12–14].

Like other NMS in PD, pain may be relatively under-reported and overlooked in clinical practice [14, 15]. SFN is also prevalent in PD [4].

The impact of pain and its specific subtypes on PD QoL has not been fully elucidated, nor sufficiently explored using specific pain measures [16–18]. This study aimed to determine the prevalence of overall pain in idiopathic PD (IPD) and specifically, look into peripheral neuropathic pain, in comparison to healthy control subjects. We also investigated the overall effect of peripheral neuropathic pain on patient QoL.

2. Methods

This was a single-centre, case-controlled, cross-sectional study of consecutive patients with IPD attending dedicated movement disorder clinics.

2.1. Study group

Patients with clinically confirmed IPD meeting the relevant diagnostic criteria [19] were identified and recruited. Individuals without IPD participated in the study as controls.

A history of possible risk factors and comorbidities that could contribute to the presence or development of neuropathic pain was elicited from both PD patients and healthy control participants. Subjects with personal and family history of neuropathy, diabetes, thyroid disease, cancer, coeliac disease/gluten sensitivity and excessive alcohol consumption were excluded from this study.

All patients and controls provided informed consent for participation. Ethical approval for the identification and recruitment of such patients was received from the NHS Health Research Authority (IRAS220562), and the University of Sheffield institutional ethics review board.

2.2. Data collection and outcome measures

For IPD patients; demographic data, the age at PD symptom onset, age at diagnosis, and start date of levodopa therapy were obtained. Reviews of patient drug charts and clinical notes were conducted to calculate the total cumulative levodopa dose each patient had received from initiation and the duration of use. The current medication regime for PD including dosage was also recorded. A levodopa equivalent dose (LED) was calculated for each patient with PD at the time of recruitment using standardised LED formulae as described by Tomlinson et al. [20]. This comprised the patients' daily dose of anti-parkinsonian drugs converted into a subtotal LED by the respective drug conversion factor. The individual subtotal LEDs were summed to give the total daily LED.

Hoehn and Yahr (HY) score was given for each IPD patient. The H& Y scale is an assessment scale validated for PD, used to compare groups of patients and provide gross assessment of disease progression [21, 22].

The Kings Parkinson's Pain Scale (KPPS) was used to assess pain in the IPD patient and control groups. The KPPS is a validated scale used to identify and grade the various types of pain in PD, developed as the first specific pain rating scale for PD patients [23]. The scale considers the location, severity, and frequency of pain across seven domains addressing pain syndromes identified in PD. The seven domains classify musculoskeletal pain (domain 1) and chronic pain (domain 2) as nociceptive pains. Neuropathic pain is considered in domains 2 and 6 (visceral pain and burning pain associated with oedema/or dopaminergic treatment). The scale also assesses “Fluctuation-related” pain, nocturnal pain (such as pain related to restless legs syndrome), orofacial pain and radicular pain. The total score indicates the overall burden of pain in PD while each domain score allows the determination of the type of pain present in each patient [23].

To assess peripheral neuropathic pain, we utilized three items of the Michigan Neuropathy Screening Instrument (MNSI) addressing hyperalgesia (Item 3, ‘*Are your feet too sensitive to touch?*’), allodynia (Item 6. ‘*Does it hurt when the bed covers touch your skin*’) and burning pain (Item 2. *‘Do you ever have any burning pain in your legs and/or feet?’*), in addition to the radicular pain domain of the KPPS [24–26]. The MNSI is used widely for the evaluation of distal symmetrical peripheral neuropathy and comprises a 15-item questionnaire and a lower extremity examination that includes inspection and assessment of vibratory sensation and ankle reflexes [27]. These can be used separately as they show similar abilities in predicting confirmed clinical neuropathy [28] but further, each of the 15 items show very high specificity individually, meaning that the absence of a correspondent symptom, identified by the questionnaire, can exclude a diagnosis of peripheral neuropathy [29].

The impact of pain on health-related quality of life was evaluated using the 36-Item Short Form Survey (SF-36), a self-reported measure of health status and health- related quality of life [29–31]. This survey scores across eight health and QoL domains of the preceding 4 weeks. These domains include physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health. Each item is measured using a Likert-type scale. Scores were converted and analysed according to the procedure for the SF-36 [30], such that higher scores (out of a total of 100 for each domain) constitute better health-related quality of life.

2.3. Statistical analyses

Frequencies and descriptive statistics were examined for the presence of pain in general and peripheral neuropathic pain in particular in IPD and control cohorts. Comparisons between PD patients and healthy controls were made using Mann-Whitney's *U* test for non -parametric continuous data, Student's *t*-test for parametric continuous data and chi-square or Fisher's exact test for categorical data.

Where statistically significant correlations or differences were found, these variables were entered into a multiple linear regression model in order to examine the relationships between these independent variables and the SF-36 sub-categories (set as the continuous dependent variable) to assess their impact on QoL. The level of statistical significance was set at 0.05.

3. Results

3.1. Study population

Fifty-one patients with IPD and 51 age and gender-matched controls were recruited. Mean age of PD patients was 68.3 ± 8.4 and for healthy control subjects 66.9 ± 10.1 years ($p = 0.445$). Gender distribution was identical in both groups with 37 of 51 (72.5%) participants being male (Table 1). The median HY score for the whole PD population was 2 (interquartile range 1.5–2.5).

3.2. Pain and quality of life in IPD patients and healthy control participants

In total, 45 IPD patients (88.2%) reported pain as captured by the KPPS (scoring above 0 in the total score) and the MNSI. This value did not differ significantly ($p = 0.487$) compared to age and sex matched controls as 48 controls (94.1%) also reported pain. However, patients with IPD presented with more severe pain in fluctuation-related (4.9 ± 6.9 vs 1.1 ± 2.6, $p < 0.001$), nocturnal (6.6 ± 7.5 vs. 1.7 ± 4.2, $p < 0.001$) and oro-facial (0.6 ± 2.0 vs 0.0 ± 0.0, $p = 0.040$) domains of the KPPS compared to controls.

In addition, when looking specifically into peripheral neuropathic