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Investigation of itch in Parkinson disease

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Introduction: Sensory abnormalities (eg, pain) are common in Parkinson disease (PD) with a negative impact on quality of life. As itch is less studied in PD, and pain and itch partially share sensory pathways, we designed this study to identify the occurrence and pattern of spontaneous itch, and responsiveness to a surrogate itch model in PD.

Methods: The study protocol was approved (N-20180079) and PD patients and their best matched controls were recruited. A questionnaire was used to collect general information on itch. Sensory alterations were determined by subjective ratings and mechanical sensitivity threshold before and after a standard histamine-dependent itch model on forearms. Itch and pain intensities were rated on visual and numerical rating scales, respectively. Dispersion of itch was drawn on arm charts. Presence and area of alloknesis and hyperknesis were determined. Group comparisons were performed in SPSS with a significant level of 0.05. Descriptive statistic was used for questionnaire's analysis.

Results: Patients (n = 20; 68.10 ± 7.91 y, F/M ratio: 8/12) and controls (n = 20; 67.35 ± 7.65 y, F/M ratio: 8/12) were examined. PD patients rated less physical and emotional descriptors, except for the stinging ($P = 0.028$). No difference was found between the groups in histamine-provoked itch intensity ($P = 0.799$) or the itchy area. A significantly larger area of hyperknesis was found in PD ($P = 0.011$), but not for the area of alloknesis ($P = 0.221$). Sex-related responses yielded only a tendency toward higher responses in female patients.

Discussion: PD does not seem to influence perception of itch, neither spontaneous nor evoked itch, except for hyperknesis area, which was found significantly larger in PD patients following the application of histamine. This finding proposes a potential alteration in central processing of itch that needs further investigation and whether and how it is affected by, for example, PD pathogenesis.

Keywords: Itch, Parkinson disease, Histamine, Quantitative sensory testing, Alloknesis, Hyperknesis

Parkinson disease (PD) is one of the most common neurodegenerative disorders, most frequently affecting individuals over 65 years[1,2], and it is characterized by motor symptoms, such as bradykinesia, resting tremor, rigidity, and postural instability, which are linked to loss of dopamine[3,4]. Nonmotor symptoms (NMS) are also present such as olfactory dysfunction, sleep problems, constipation, depression, and pain[5,6]. These symptoms often precede motor symptoms[7] and might serve as a useful tool for early diagnosis. Pain is one of the most studied sensory alterations that affects from 30%–95% of PD patients[8,9]. It remains to be elucidated, but loss of dopamine and dysfunction of the basal ganglia have been linked to pain in PD[6,8,10,11]. Allodynia and hyperalgesia are also present in PD[12] and are proposed as features of hypersensitivity within the central nervous system (CNS). Only a few studies have used quantitative sensory testing in PD. A lower threshold in response to the cold pressor test and a lower pressure pain threshold have been found in PD patients[13]. Sung et al[14] have also found a reduced pain threshold and an increased pain sensitivity in PD patients. Andersen et al[15] found a significant difference in PD patients compared with controls in response to brush and pinprick stimuli on the forearms and lower back. Considering the literature about pain and PD, and the fact that itch and pain partially share sensory pathways[16–20], it is not unexpected to speculate that presence and sensation of itch might also be different in PD patients. Itch, similar to pain, can pose a negative impact on quality of life[21], in particular, in the aged population, who may also have PD. Generally, dermatological conditions that can accompany itch are present in PD[22]. Skin disorders and senile pruritus are common in the elderly population[21,23]; hence, it can be difficult to distinguish a neurological etiology from a dermatological one (eg, seborrheic dermatitis, melanoma, and rosacea[22]), which can further complicate investigation of itch in PD.

The phenomenon of itch, however, has not been studied in PD. Therefore, the purpose of this study was to determine if spontaneous itch was in fact present in PD patients without evidence of a dermatological condition. It was hypothesized that PD patients would present a different occurrence and pattern of general itch

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compared with controls. We also hypothesized that a standard experimental itch model could provoke itch sensation in both PD patients and controls, but potentially with different characteristics. Experimental itch models[24,25], histamine-dependent and histamine-independent[26], have been developed and used in the literature for different purposes, such as understanding itch mechanisms and responsiveness to antipruritic drugs[27,28]. We applied 1% histamine model to assess the intensity of the provoked itch and to quantify sensory alterations[29]. We hypothesized that PD patients would present a different histamine-evoked response in terms of itch intensity, size of the itchy area, and manifestations of central sensitization (alloknesis and hyperknesis) compared with non-PD controls.

Methods

An experimental, parallel-group, open study was performed on PD patients and their best matched controls [in sex and age (± 5 y)]. The subjects participated in one experimental session lasting ~75 minutes. The study protocol was approved by the North Denmark Region Committee on Health Research Ethics (N-20180079) and conducted according to the Declaration of Helsinki, 2013 and Good Clinical Practice (GCP) guidelines. The study was conducted in 2019 at the Neurology Department, Aalborg University Hospital, Denmark.

Subjects

Idiopathic PD patients were recruited in collaboration with physicians affiliated at the Department of Neurology, Aalborg University Hospital, Denmark. Best matched controls were recruited through public notices and online advertisement in the Facebook. Subjects, who showed interest in participating, received written information about the study and had the opportunity to ask questions before committing to participate. Before testing, written informed consent was obtained from all participants. Thereafter, all participants were screened for inclusion and exclusion criteria. Only control group participants were compensated for the time of their participation, which was approved by the ethics committee.

All included PD patients were within the age range of 50–85 years, diagnosed with idiopathic PD within 2–10 years, had an acceptable cognitive function [Mini Mental State Examination (MMSE) > 24], Caucasian, and could understand and speak Danish. PD patients were excluded if they suffered from other peripheral or CNS disorders, musculoskeletal or psychological conditions; liver or renal conditions; diabetes; any present or previous dermatological or allergic disorders; addicted to drugs like cannabis, opioids or other drugs; had consumed alcohol for the last 24 hours; used medication with impact on the immune system or pain for the last 24 hours; had tattoo, scare, wound at the volar side of the arm; and if lacked the ability to cooperate.

MMSE was used as a screening tool to investigate the cognitive state of the participants. This was performed to ensure that the participants understood the experimental procedure for the study. The MMSE was firstly introduced by Folstein et al[30] as a shortened and simplified version of the cognitive mental status examination. It is possible to achieve a total of 30 points in the MMSE, and a score of 23 or less has generally been accepted as an indicator of cognitive impairment[31].

The controls were matched in terms of sex and age (± 5 y) with the PD group. Otherwise, the inclusion criteria were similar to PD patients, with the exception of the PD diagnosis. Regarding the exclusion criteria, the best matched controls were excluded if they suffered from any peripheral or CNS disease, musculoskeletal or psychological conditions, and otherwise for the same reasons as PD patients.

Experimental procedure

The experimental procedure is depicted in **Figure 1**.

The first part consisted of a screening session to check the inclusion-exclusion criteria and to obtain descriptive data of the study population. In addition, MMSE scores and the history of itch perception were recorded.

A circle with a diameter of 8 cm was drawn in the middle of the volar surface of the dominant forearm for the mechanical sensitivity threshold (MST). The dominant forearm was defined as the arm of the most PD-affected side in patients, whereas in the best matched control group the side was the actual dominant forearm.

For the baseline assessment of sensory perception, in the middle of the marked area, a light touch test was done with a cotton swab, followed by pinprick stimulation to determine the MST.

Afterwards, histamine was applied to the middle of the marked area to provoke itch. The participants were asked to rate their itch on a visual analog scale (VAS) and their pain on a numerical rating scale (NRS) every 30 seconds. The value 0 indicates "no itch/no pain" and the value 10 indicates "the worst imaginable itch/pain." The test was completed when the itch had disappeared or after 15 minutes had passed.

Thereafter, the areas of alloknesis, hyperknesis, and perceived itch were assessed. While the alloknesis and hyperknesis were mapped using, respectively, cotton swabs and pinpricks, the dispersion of perceived itch was drawn on an arm chart. The itch dispersion was an attempt toward finding the graphical pattern of itch presentation. The idea was formed based on a recent study in pain[32], which has proposed that this method can help in screening of pain in patients.

During the sensory testing, the participants were instructed to look away or close their eyes. All procedures were performed by the study investigators following predefined standard operating procedures. All data were recorded in the Case Report Forms (CRFs) and organized in Excel sheets for further statistical analysis.

Tests

Questionnaire to examine the history of itch perception

With the custom-made questionnaire, the participant's experience with spontaneous itch was investigated. This included identification of perception, history, and patterns of itch. The questionnaire was developed in Danish, tested in a pilot trial, and approved by the ethics committee. It was made with inspiration obtained from two validated questionnaires, "Eppendorf Itch Questionnaire"[32] and "McGill Pain Questionnaire"[33]. The custom-made questionnaire consisted of two parts. Part A consisted of 70 different descriptors and was filled out by each subject. The first 35 descriptors described the physical sensation of itch, whereas the last 35 descriptors described the emotional sensation of itch. The different descriptors were scored on a scale of 0–4; 0 being "not true" and 4 being "describes my sensation of itch exactly." Part B consisted of different questions about the

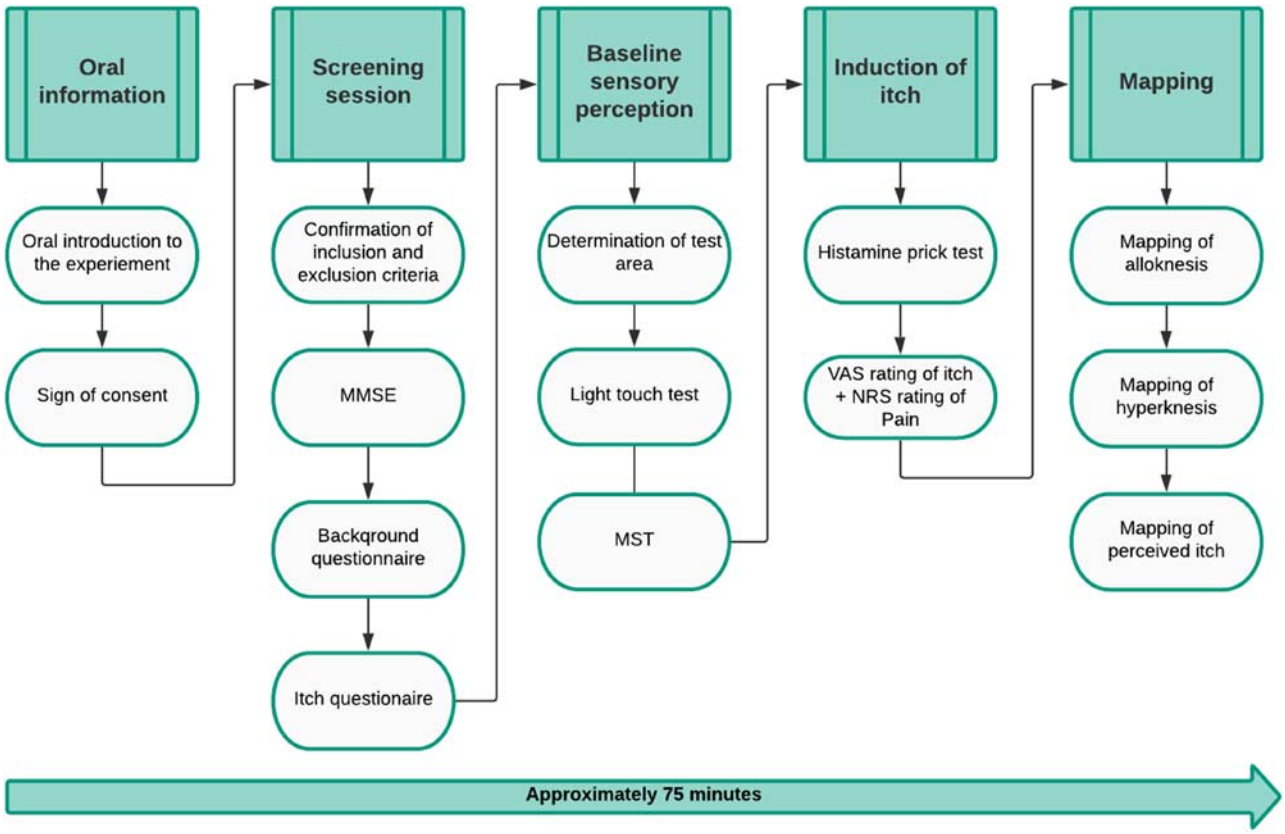

Figure 1. Overview of the experimental procedure, including tests, order of tests, and timeline. MMSE indicates Mini Mental State Examination; MST, mechanical sensitivity threshold; NRS, numerical rating scale; VAS, visual analog scale.

location and duration of itch, and explored strategies to avoid or relieve itch. In addition, the location of itch was marked on a full body drawing. Part B was filled out by the investigator entering the answers from the participants. The questionnaire overall was used to compare the perception of itch in the 2 groups and to determine if a general difference in the feeling of itch existed between the PD patients and the controls before the experimental procedure.

Light touch test

At baseline, a light touch test was performed using cotton swabs (Wood Hospital Applicators, Mediq, Brøndby, Denmark) to test the responsiveness to the light touch, which is usually used to test the perception of tactile touch input[34]. The light touch test was performed with the purpose of testing if any sensory disturbances were present within the test area and if the touch of the cotton swab could be felt as normal or absence of tactile sensation, itch, or pain. Please note that this test was to dab the skin rather than stroking it. In cases of feeling itch or pain, the participants had to rate the itch on the VAS (0–10) and the pain on the NRS (0–10). 0 indicated "no itch/pain," and 10 was "the worst imaginable itch/pain." These scales helped subjects to stay clear for the rating of the 2 different sensations of pain and itch and to avoid confusion. The light touch test was repeated 3 times and averages of VAS and NRS scores were recorded.

Assessment of MST

MST is used to determine the threshold of sensitivity to mechanical stimuli such as pinpricks[32] that activate the Aδ-fiber and C-fiber[35]. In this study, the purpose of the MST was to determine the individual's threshold of sensitivity and the occurrence of sensory abnormalities. This test is usually used to identify hyperalgesia or hyperknesis[29]. Seven different weighted pinprick stimulators (MRS systems GmbH, Heidelberg, Germany) were used. The pinpricks (blunt needles with a fixed stimulation intensity of 8, 16, 32, 64, 128, 256, and 512 mN) were applied perpendicular to the skin in ascending-descending order, followed by descending-ascending order, based on a standard procedure[32]. This procedure was repeated 3 times and the MST was calculated using the weight of the pinprick the first time where the subject detected a difference in the sensory perception.

After each prick, the subject was asked to rate the itch on the VAS, rate the pain on NRS, and indicate if there was a noticeable change in sensory perception between the pricks. The averages for itch and pain were also calculated.

Application of histamine

To investigate the responsiveness to a standard evoked itch between PD patients and controls, the histamine-dependent itch model was used by the application of histamine on the disinfected and dried volar surface of the dominant forearm. If the subjects

had any pain or itch sensation before application of histamine, it was rated on the related scales and recorded.

One drop of 1% histamine dihydrochloride (ALK-Abelló Nordic A/S, Hørsholm, Denmark) was placed on the test area, and a finger pricker (Softlance "Fingerprikker": Mylife, Bionime Corporation, Taichung City, Taiwan) using 0.32 mm lancets (Soft Fine Colour, REF 110, Klinion, Medecon B.V., The Netherlands) was used to permit histamine reaching into the epidermis. Each subject rated the evoked itch on a VAS and pain intensity on an NRS, every 30 seconds. The average VAS score of the itch and the average NRS score of pain were calculated and used for further statistical analysis. The experiment ended when the histamine-induced itch disappeared, or 15 minutes after application of histamine, or when the last 3 readings were below 1 following ≥ 3 subsequent rating.

Mapping and assessment of dysesthesia

Itch dysesthesia is defined as an uncomfortable abnormal sensation, which induces itch by light stimuli and is described in terms of alloknesis and hyperknesis[29]. These areas together with the perceived itchy area were mapped.

Alloknesis was assessed with brushing skin lightly by a cotton swab starting at one of the outer marks of the octagon (4 cm from the histamine application site) and moving in intervals of 0.5 cm toward the application site. This was repeated for all the outer marks, and the area was mapped by 8 horizontally arranged paths. The subject was instructed to report when the application of the cotton swab changed to a feeling of itch. The site of the change in perception was marked, the identified points on each path were connected and scanned, and the area (cm^2) was quantified using Vistametrix (Version 1.38, Skillcrest, Tucson).

Hyperknesis was determined with the individual MST. This was done as described above on the octagon and the subject was instructed to report when the prick sensation was changed to noticeably more itch or other sensory feeling. Areas of hyperknesis were then quantified by tracing and measurement of the area with the aid of Vistametrix.

Finally, the subjects were asked to draw the area of their perceived itch on an arm chart. The drawings from the PD patient group and the control group were superimposed separately to investigate the pattern of dispersion following histamine provocation. The areas were then digitized and quantified (cm^2) using Vistametrix.

Data analysis

In this study, flowcharts were created using Lucidchart (Lucid Software Inc., South Jordan, Utah). Microsoft Excel [Microsoft Excel for office 365 MSO (16.0.12130.20232)] was used to organize data, and GraphPad Prism (version 8.1.0 2018) was used to construct graphs to visualize the data. Vistametrix (Version 1.38, Skillcrest, Tucson) was used to quantify the area (cm^2) of alloknesis, hyperknesis, and dispersion of itch on the arm chart. Data are presented as arithmetic means $\pm$ SD or as median and the interquartile range (Q1Q3).

G*Power (Version 3.1.9.2, Franz Faul, Kiel University, Germany) was used to calculate the power. Initial sample size determination in the study protocol was based on a published study[15] conducted to identify pain and other sensory disturbances, with 80% power that yielded 40 participants.

Statistical Package for Social Sciences Software (SPSS) (IBM SPSS, version 26, Armnok, New York) was used to determine if the data were normally distributed using the Shapiro-Wilk. On the basis of this, parametric or nonparametric ways for data presentation and tests for comparisons were followed. All statistical tests were considered significant at a P-value ≤ 0.05.

Questionnaires regarding the history of perceived itch were analyzed. The most frequently used physical, sensory, and emotional descriptors were selected, and the mean and SD were calculated. Bar charts were constructed to illustrate the frequency (%) and the mean ratings of the most used sensory and emotional descriptors. The ratings of these descriptors were compared using Mann-Whitney U tests, for non-normally distributed data, and 2-samples independent t test, for normally distributed data. The Levene test was completed to meet the assumption of homogeneity of variances for the 2-sample t test. Levene test results presented homogeneity of variances where a P-value above 0.05 was found.

The locations of itch from the body charts were superimposed on transparent papers to investigate if a pattern was observed. Finally, the intensity of itch was rated on a visual scale, which was converted to a scale from 0 to 10 to investigate the different itch intensities in the 2 groups. Mann-Whitney U test was used to compare these itch intensities to determine if a significant difference was observed.

All data from the different sensory tests (light touch test, individual MST, histamine response) were used to investigate if a difference between the 2 groups was present. To compare the VAS for itch and NRS for pain, respectively, 2-sample independent t-tests were performed on normally distributed data, and Mann-Whitney U tests were performed on non-normally distributed data. Area under the curve (AUC) was calculated for the VAS-time curve of histamine-provoked itch and the NRS-time curve of histamine-provoked pain for both groups. AUC was used to identify an overall sensation of itch and pain, considering both intensity and duration of these sensations to provide further information in addition to the peak intensity and the duration, separately.

Moreover, Spearman correlation analysis was performed for itch intensity and, respectively, to find out if disease duration and age could be correlated with this. The rationale behind the test was that it has been reported that age and neurodegenerative diseases can alter the 5 senses[36]. Moreover, 2-sample independent t tests were used to investigate if any difference in histamine-provoked itch intensity was observed between male and female participants, based on the literature pointing to the potential of sex-based responses in itch[37,38].

The areas of alloknesis, hyperknesis, and the dispersion of itch on the arm chart were quantified in Vistametrix. Mann-Whitney U test was used for each area to investigate if any difference was observed between the PD patients and controls. The dispersion of perceived itch was also superimposed to examine if a pattern could be distinguished.

Results

Subjects

Eighty PD patients and 38 controls were recruited for participation in the study. Eighteen PD patients and 5 controls declined to participate, and 42 PD patients and 13 controls were excluded as

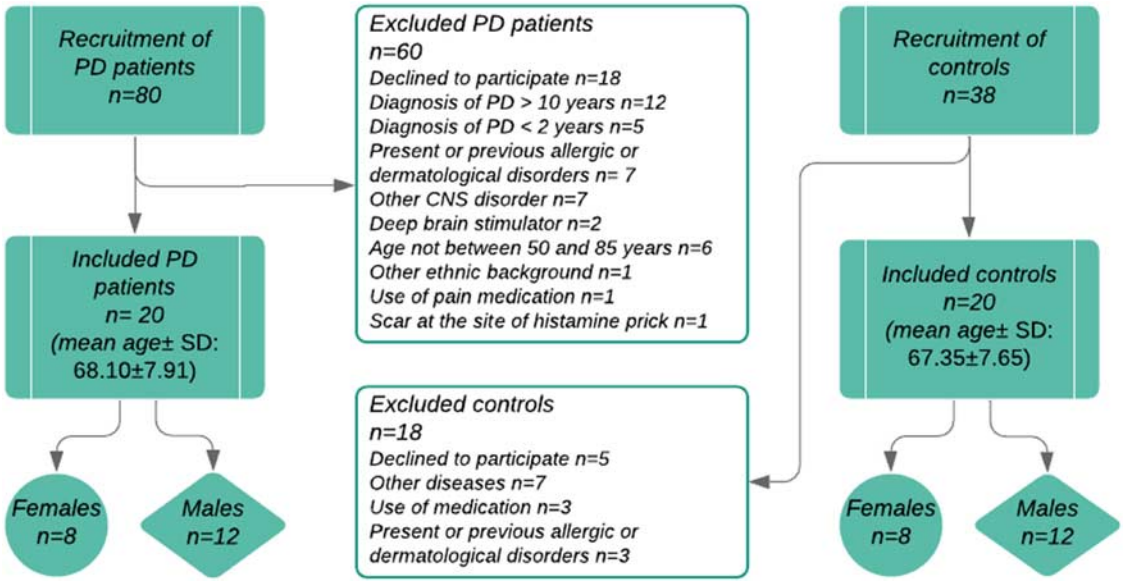

Figure 2. Flowchart of the recruitment of study participants, which consisted of 2 groups; PD patients and best matched controls. When all inclusion and exclusion criteria were fulfilled, 20 PD patients and 20 controls were included in the study. Age is indicated in years. CNS indicates central nervous system; PD, Parkinson disease.

they did not meet the criteria. Therefore, the study population consisted of 20 PD patients and 20 best matched controls with 8 females and 12 males in each group. The mean age ± SD was 68.10 ± 7.91 years in the PD group and 67.35 ± 7.65 years in the control group (**Fig. 2**). An independent 2-sample *t* test found no significant difference in age between the 2 groups ($P = 0.792$).

Table 1 shows the demographic and clinical characteristics of the PD patients and the control group. The included PD patients had on average a disease duration with a PD of 6.33 ± 2.55 years and they all were treated with PD medications (Levodopa preparation: Madopar, Madopar Quick, Stalevo, Levo-dopa, Sinemet. Dopamine agonist: Ropinirol, Oprymea, Sifrol, Sifrol depot. Monoamine Oxidase B inhibitor: Rasagilin). One PD patient was on dopamine agonist monotherapy. Eight PD patients only received levodopa treatment, while the remaining 11 received levodopa treatment in combination with other PD medications (**Table 1**). In addition, the interval between intake of medication was different among the patients; 1 PD patient only took medication once a day, while others used it up to 8 times per day. Finally, the subjects were asked if they had or had had any problems with itch throughout life. In all, 40 % of the PD patients and 35% of the controls reported previous or present problems with itch.

Table 1

Demographic and clinical characteristics of PD patients and controls.

	PD Patients (n = 20)	Controls (n = 20)
Age (y)	68.10 ± 7.91 (54–81)	67.35 ± 7.65 (52–77)
Sex (female/male)	8/12	8/12
Dominant arm (right/left)	14/6	19/1
MMSE	29.40 ± 0.99 (26–30)	29.70 ± 0.66 (28–30)
Disease duration (y)	6.33 ± 2.55 (2–10)	—
Age of onset (y)	61.78 ± 9.03 (45–79)	—
PD medication		
Levodopa (%)	90	—
Dopamine agonist (%)	40	—
MAO-B inhibitor (%)	25	—
Presence of itch (%)	40	30

Note: several PD patients received more than one type of PD medications.
MAO-B indicates monoamine oxidase-B; MMSE, Mini Mental State Examination; PD, Parkinson disease.

Questionnaire

Previous or present experiences with itch

All subjects, regardless of past or present itch problems, were asked to fill out a Danish questionnaire.

The questionnaire was used to investigate, which physical, sensory, and emotional descriptors the participants used to describe the sensation of itch. The subjects who did not have any problems with the itch were told to think about the feeling of a mosquito-bite if facing difficulties to answer the questions. The frequency of the most used physical and emotional sensory descriptors is summarized in **Table 2**.

The participants also indicated general and major locations of their itch experience in the past. The body charts were superimposed and are presented in **Figure 3**. In general, especially, the shin was a frequent itch location, but the chest, back, and the scalp were also common places for the sensation of itch in the study population. No clear pattern was observed in either group.

Age-based responses

The literature presents that the elderly population are prone to itch associated with age-related changes that occur in the skin, some comorbidities and medication use, and psychological conditions[39,40]. To investigate if any difference existed in the spontaneous intensity of itch, reported based on the age, the

Table 2

Summary of the itch history questionnaire.

	Frequency (%)		Mean Ratings ± SD	
	PD	C	PD	C
Sensory descriptors				
Pricking	55	55	1.91 ± 0.94	1.64 ± 0.81
Give the creeps	40	30	2.75 ± 0.71	2.67 ± 1.37
Like sunburn	40	25	2.25 ± 0.89	1.60 ± 1.34
Stingning	35	65	1.71 ± 0.76	2.53 ± 1.05
More when warm	45	45	2.33 ± 1.00	2.00 ± 1.00
Mosquito bite-like	35	45	2.29 ± 0.75	2.67 ± 0.87
Itching	50	80	2.90 ± 1.29	2.56 ± 1.15
Palpable	50	40	2.20 ± 0.92	2.00 ± 0.75
Emotional descriptors				
Bothering	80	90	2.38 ± 1.02	2.06 ± 1.21
Annoying	65	85	2.08 ± 0.95	2.41 ± 1.18
Unpleasant	45	60	2.56 ± 1.13	2.5 ± 1.09
Disturbing sleep	20	35	1.25 ± 0.50	1.71 ± 0.49
Disturbing in general	30	40	2.50 ± 1.22	1.78 ± 0.97
Scratch behavior				
Scratching	65	80	2.23 ± 1.01	2.13 ± 0.96
Rubbing	35	50	2.29 ± 0.95	2.20 ± 0.79
Company distracts	35	45	1.71 ± 0.95	2.77 ± 0.97
Gives satisfaction	70	65	2.29 ± 1.27	2.38 ± 0.96
Decreases itch	50	45	2.20 ± 1.14	2.33 ± 1.12

The frequency in % of the most selected physical sensory descriptors, emotional descriptors, and descriptors related to scratch behavior of Parkinson disease patients and controls are presented. The mean ratings (rated from 0 to 4) ± SD of these descriptors are shown.
C indicates controls; PD, Parkinson disease.

median of age for all participants was calculated and the following age ranges were determined; the younger age range was 52–68 y and the older age range was 69–81 y for PD patients and controls. The Mann-Whitney *U* test showed no significant differences between the PD patients and controls in the lower or the higher age range. The Mann-Whitney *U* test was also used for within-group comparison, which demonstrated no significant difference between PD patients in different age ranges ($P = 0.739$) or between the controls ($P = 0.436$).

Sex-based responses

A mixed outcome has been presented in the literature with regard to sex differences in itch. However, a general finding is that in chronic pruritus, itch characteristics, for example, itch intensity, are higher in females[37,38,41]. Our population included both females (16) and males (24). Therefore, we analyzed data to see if any sex-related responses existed in 4 groups of PD males, PD females, control males, and control females. The Kruskal-Wallis test found no significant difference in *scratching* between any of the 4 groups ($P = 0.826$).

The ratings of *company distracts* as a way to deal with the sensation of itch were lower in males with PD compared with the control males. The median was 1.0 (1.0–1) for males with PD and 3 (1.5–3.0) for the control males. The opposite was observed among the female participants; the median was 2.0 (1.0–3.0) for females with PD and 3.0 (2.0–4.0) for females of the controls. When comparing males and females in the 2 groups, no differences were found (Kruskal-Wallis test comparing the 4 groups, $P = 0.826$).

The ratings of *gives satisfaction* in relation to scratching the itch did not present any significant difference where medians were compared with the Kruskal-Wallis test ($P = 0.824$). The Kruskal-Wallis test found no significant difference in the ratings of *scratching decreases itch* between any of the 4 groups either ($P = 0.266$).

The ratings of the *past itch intensity* were also investigated in relation to sex. The median VAS was 3.0 (2.0–5.0) for the males with PD and 3.5 (1.0–7.0) for the males in the control group. A lower past itch intensity was observed among the female PD patients [2.0 (1.0–6.75)] compared with the females in the control group [5.0 (3.0–6.75)]. Comparing the males and females in both groups, the females in the control group had the highest median. However, the Kruskal-Wallis test found no

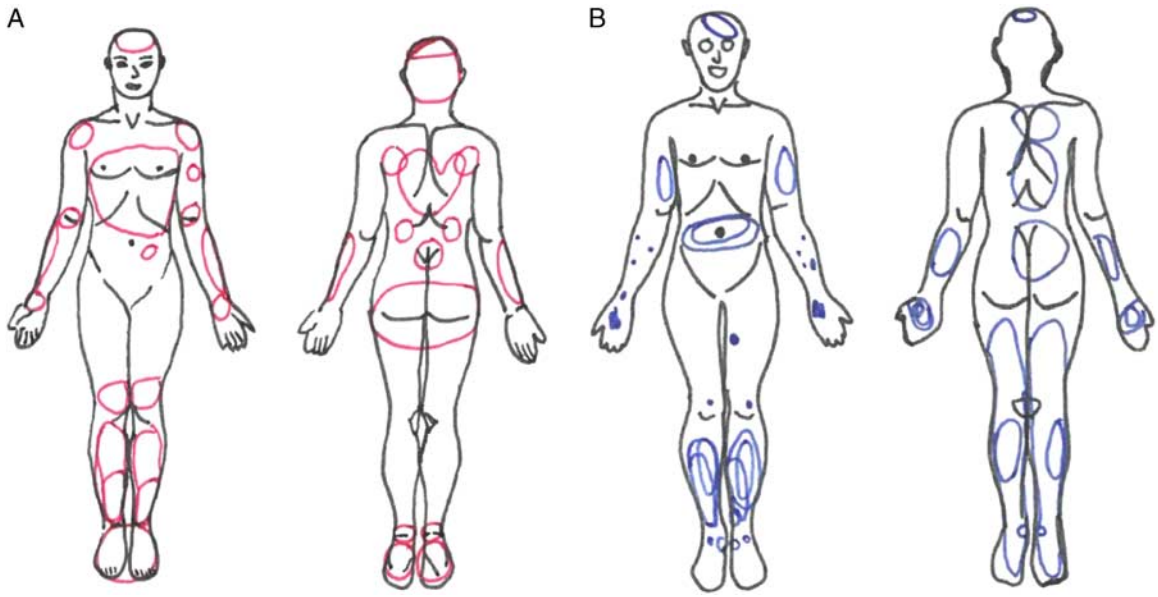

Figure 3. A, Body charts illustrating localization of itch in patients with Parkinson disease and (B) in controls.

significant difference in itch response between the 4 groups ($P = 0.471$).

Mechanical sensitivity

To investigate if the participants had any presence of alloknesis on their dominant forearm, a light touch test was performed. One of the PD patients had an average itch sensation of 0.2 ± 0.35 on the VAS, while another PD patient had a mean pain sensation of 0.67 ± 1.2 on the NRS. None of the controls had any sensations of itch or pain with the touch of cotton swabs. The Mann-Whitney *U* tests found no significant difference between the PD patients and the controls regarding itch sensation ($P = 0.317$) and pain sensation ($P = 0.317$) in relation to the light touch test.

To investigate the presence of hyperknesis in PD patients and controls, the individual MST was used on the dominant forearm. The median MST in PD patients was 162.09 (122.67–298.67) mN, while the median of the controls was 165.34 (102.67–234.67) mN. The Mann-Whitney *U* test found no significant difference in the mean MST between PD patients and controls ($P = 0.543$). The presence of hyperknesis was investigated with itch ratings on a VAS during the assessment of MST. During the pinprick test, the occurrence of itch was observed in 6 (30%) of the PD patients and in 2 (10%) of the controls. The Mann-Whitney *U* test found no significant difference in hyperknesis between the 2 groups ($P = 0.126$).

In addition, the 2 groups had to rate pain on the NRS during the MST. The occurrence of pain was observed in 12 (60%) of the PD patients and in 11 (55%) of the controls. The Mann-Whitney *U* test found no significant difference in the rating of pain during the MST determination between the 2 groups ($P = 0.455$).

Histamine response

The application of histamine was performed on the dominant forearm. On average, the duration of itch was 8.35 ± 3.89 minutes for the PD patients and 8.38 ± 3.56 minutes for the controls. However, 1 control already felt the itch before the histamine application, and 2 controls and 1 PD patient did not feel any itch after the histamine application.

Figure 4A illustrates the itch response in relation to histamine application over time for PD patients and controls.

The median VAS rating of itch was 1.04 (0.47–1.84) for the PD group and 1.2 (0.68–1.89) for the controls. The Mann-Whitney *U* test found no significant difference between the PD group and the control group ($P = 0.799$). In addition, AUC was calculated for the VAS-time curve of the PD group (AUC = 881.7 mean itch VAS × minutes) and the control group (AUC = 870.15 mean itch VAS × minutes). However, no significant difference was found between the 2 groups either.

The Mann-Whitney *U* test was also performed on peak of itch intensity, and no significant difference was evident between the groups ($P = 0.88$). The time to reach to the peak itch intensity was also determined, which was 150 (60–240) seconds for the PD patients and 165 (150–210) seconds for the controls. The Mann-Whitney *U* test showed no significant difference in the time to reach to the peak itch intensity between PD patients and controls ($P = 0.547$).

Furthermore, during the application of histamine, the 2 groups were asked to rate pain on an NRS. **Figure 4B** illustrates the mean rating of histamine-generated pain in PD patients (red) and in controls (blue).

The Mann-Whitney *U* test found no significance difference in the mean of pain rating between the 2 groups ($P = 0.057$).

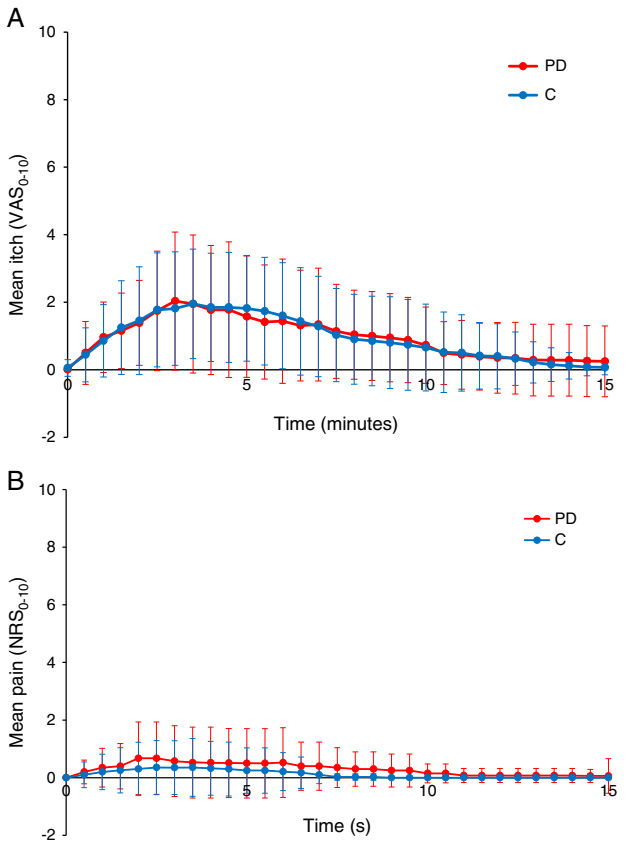

Figure 4. A, VAS-time curve of histamine-provoked itch for PD patients (red) and controls (blue). The itch intensity was rated on a VAS from 0 to 10 every 30 seconds until the itch subsided or for 15 minutes. No significant overall difference was found in the sensation of histamine-provoked itch between the 2 groups ($P = 0.921$). B, NRS-time curve of the histamine-provoked pain for the PD patients (red) and controls (C) (blue). The pain intensity was rated on an NRS from 0 to 10 every 30 seconds. C indicates control; NRS, numerical rating scale; PD, Parkinson disease; VAS, visual analog scale.

Moreover, the AUC of the NRS-time curve was 275.7 mean pain NRS × minutes in the PD group and 109.5 mean pain NRS × minutes in the control group, but no difference was found.

Age-based responses

To investigate if any difference existed in the responsiveness to histamine between PD patients and controls as a function of age, younger age range (52–68 y, N = 10) and older age range (69–81 y, N = 10) for PD patients and controls were compared. A 2-sample *t* test demonstrated no significant differences between the PD patients and controls in the lower age range ($P = 0.708$). Similarly, no significant difference between PD patients and controls for the higher age range was obtained ($P = 0.939$). To investigate differences in the responsiveness to histamine between the different age ranges within each group, an independent *t* test demonstrated no significant differences between the age ranges in PD ($P = 0.749$). Likewise, an independent *t* test demonstrated no significant differences between the controls for the different age ranges ($P = 0.369$).

Sex-based responses

The histamine-evoked itch intensity is presented in **Figure 5A** for males and females in PD and control groups. The 1-way analysis of variance found no significant difference in itch response between the 4 groups ($P = 0.482$).

Regarding pain sensation, the Kruskal-Wallis test found no significant difference in pain response between any of the 4 groups ($P = 0.094$) (**Fig. 5B**).

Age and itch responses

There was a negligible correlation between age and histamine-induced itch intensity. Spearman correlation coefficient r_s was 0.028, when it was tested for the mean of the itch intensity. The correlation was not statistically significant ($P = 0.865$). Pearson correlation analysis of the peak of itch intensity also showed no significant correlation.

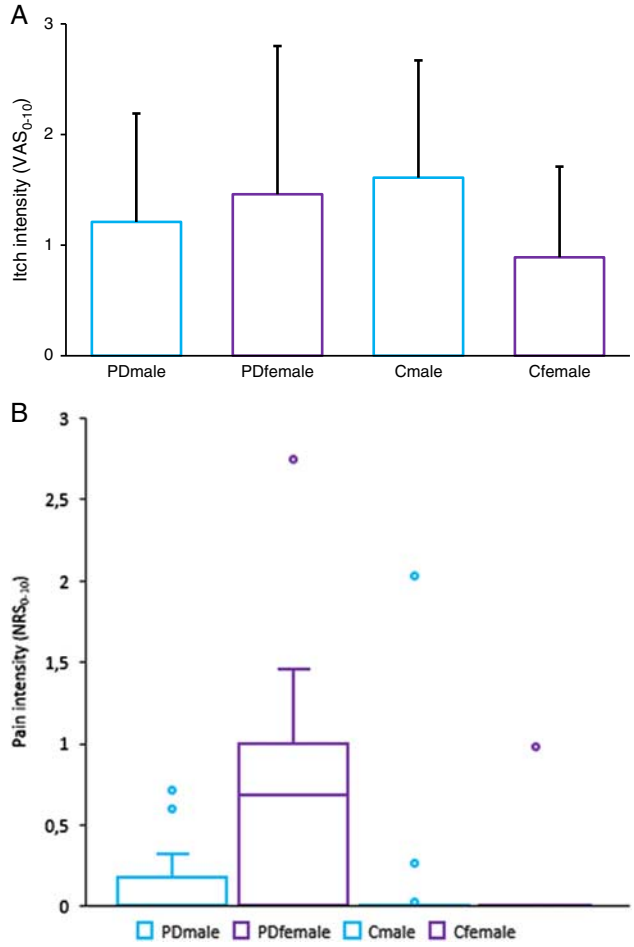

Figure 5. A, Itch intensity of the male (light blue) and female (purple) participants of the PD group and the control (C) group. The histamine-provoked itch intensity was rated on a VAS from 0 to 10 every 30 seconds. No significant difference was found between the groups. B, Box plots illustrating pain intensity for the male (light blue) and female (purple) participants of the PD group and the control (C) group. The histamine-provoked pain intensity was rated on an NRS from 0 to 10 every 30 seconds. No significant difference was found between any of the 4 groups. C indicates control; NRS, numeric rating scale, PD, Parkinson disease; VAS, visual analog scale.

Disease duration and itch responses

There was a negligible correlation between disease duration and histamine-induced itch response in PD patients, as the Pearson correlation was 0.076 ($P = 0.749$).

Areas of alloknesis and hyperknesis following histamine provocation

The presence and patterns of alloknesis and hyperknesis areas on the dominant forearm were investigated after the histamine-provoked itch had returned to 0. The areas were determined and subsequently quantified (cm^2) by Vistametrix. The box plot in **Figure 6A** demonstrates the areas of alloknesis and hyperknesis (cm^2) observed in PD and the control groups. The median area of alloknesis was 1.67 (0.75–6.35) cm^2 in the PD patients and 0.78

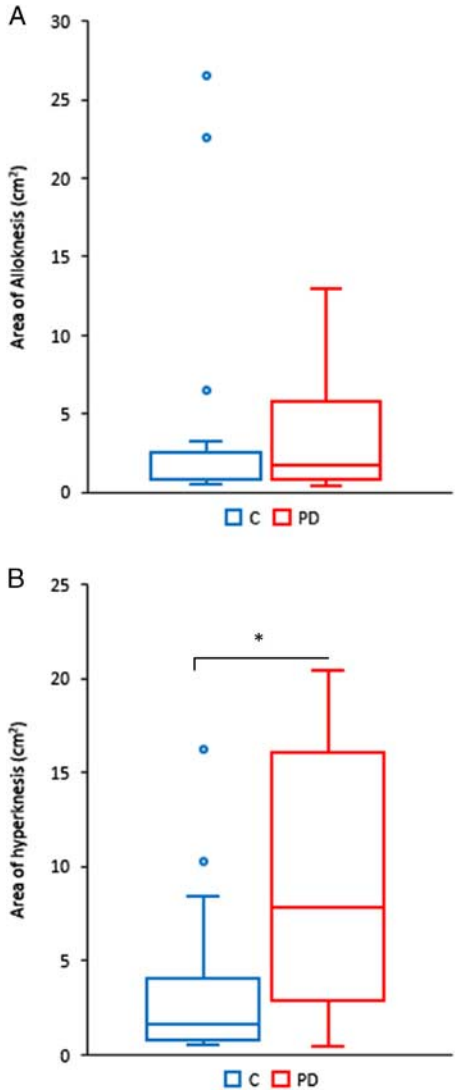

Figure 6. A, Box plot illustrating the median area of alloknesis in cm^2 in the PD group (red) and controls (blue). No significant difference was observed in the area of alloknesis ($P = 0.221$). B, Box plot illustrating the median area of hyperknesis in cm^2 in the PD group and the control group. A significant difference was observed in the area of hyperknesis ($P = 0.011$). C indicates control; PD, Parkinson disease. *$P \leq 0.05$.

(0.74–2.2) cm^2 in the control group (**Fig. 6A**). The Mann-Whitney *U* test found no significant difference between the 2 groups ($P = 0.221$).

The median of the area of hyperknesis was 7.77 (2–17.15) cm^2 in PD patients and 1.54 (0.74–5.24) cm^2 (**Fig. 6B**). The Mann-Whitney *U* test found a significant difference between the 2 groups ($P = 0.011$). This indicates that the PD patients had a significantly larger area of hyperknesis after the histamine response compared with the control group.

Itch dispersion after histamine application

The dispersion of itch following the application of histamine was traced on the arm charts and the areas (cm^2) were quantified by Vistametrix. **Figure 7** illustrates the dispersion of itch in PD patients and controls. The dominant arm was defined differently in the two groups, as it was the most affected side of PD patients, which was used for the experiment. This explains the higher number of drawings on the left arm chart in the PD group compared with the control group. **Figure 7** shows that the dispersion of itch after histamine application was more scattered and further away from the region of the histamine prick test in the PD group compared with the control group. The median area was 3.84 (0.92–6.88) cm^2 for the PD patients and 1.32 (0.28–5.75) cm^2 for the controls, and the Mann-Whitney *U* test found no significant difference between the 2 groups ($P = 0.185$).

Discussion

This study was the first to investigate patterns and characteristics of itch in PD. The main finding was a larger area of hyperknesis in response to histamine-provocation test in PD patients compared with controls.

Experiences of itch

The most frequent sensory descriptors chosen were different between the two groups, but with no significant difference. Majority of controls selected the sensory descriptors "itching" and "stinging," while PD patients selected a wider and more diverse range of words. The PD patients might have found it easier to describe the itch and relate to descriptors such as "palpable" and "give the creeps." The most frequent emotional descriptors were rated with a higher severity by the controls compared with the PD patients, but no significant difference was found. Emotional descriptors such as "bothering" and "annoying" were the most scored emotional descriptors for both groups. There was also no difference between the groups in the localization of past itch experience. Larger, population-based studies are required to delineate general perception of itch descriptors and localization in patients with PD.

Looking at data related to scratch behaviors, the two groups seemed equal in how they describe their behavior toward relief of itching. The most frequently observed method to deal with itching was scratching in both the PD group and the control group. Moreover, 70% of PD patients and 65% of controls stated that scratching their itch resulted in a satisfying feeling. This shows that both PD and control subjects act similarly in terms of scratch when feeling itch. The feeling of satisfaction correlates with the findings of Papoiu et al[27] that the act of scratching an itch is rewarding and gives a feeling of pleasure. Furthermore, we know that cognitive attention and/or distractions have a great influence on pain[42,43] perception and thereby reduce the intensity. Distraction might influence itch similar to pain, and that might be

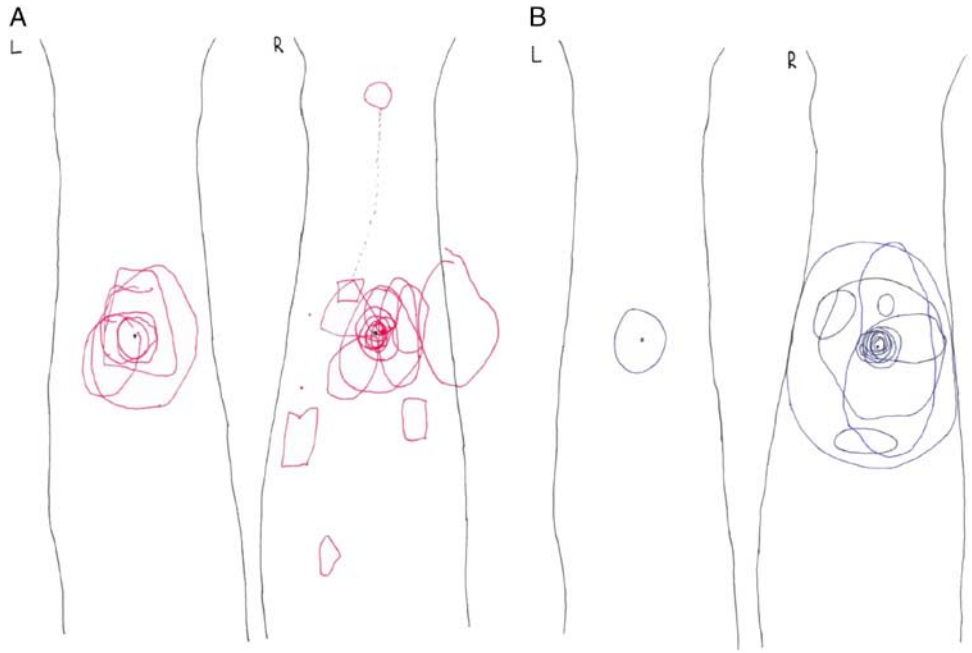

Figure 7. Arm charts illustrating localization of itch dispersion in (A) Parkinson disease (PD) patients (red) and (B) controls (C) (blue). PD: 3.84 (0.92-6.88) cm^2, C: 1.32 (0.28-5.75) cm^2. Note that the drawing outside the arm chart refers to expansion to the other side of the arm, where one patient sensed and reported it.

based on the involvement of some feelings or emotions. However, van Houtum et al[44] have reported that chronic illness could affect the energy and presence in social context, where basic and social problems in daily life were observed in one-third of the 1713 patients with chronic diseases. This might also influence PD patients. The scratch behavior was not different between male and female participants. In a former study[38], females and males, however exhibited differences in their itch perception as reflected on higher itch intensities and desire to scratch in females. However, we cannot directly compare our data with Ständer et al[38], who focused on patients with chronic pruritus under different age and disease conditions.

Of our PD patients, 40% reported previous problems with itch, which can indicate that itch is a sensory modality that affects some PD patients. However, 35% of the controls also reported previous problems with the itch. This opens a new proposal that itch sensations can be explained by other factors such as vitamin deficiency or being of old age, as previous studies have found a high occurrence of pruritus conditions in the elderly population[23,45,46]. To test this, we sub-divided participants into 2 age groups: younger age group (52–68 y) and older age group (69-81 y). However, comparison of these 2 groups did not show any significant difference.

Mechanical sensitivity

This study found no baseline presence of alloknesis or a difference of developed alloknesis following the histamine-evoked itch between the 2 groups of PD and controls. The presence of alloknesis in PD patients has not previously been investigated; therefore, there is not a base for comparison, and the potential mechanism cannot be ruled out with the method and measurements of this study. However, Andersen et al[15] found dynamic mechanical allodynia in 58.33% of PD patients with a brush test.

We did not find hyperknesis at baseline, but the PD patients had a significantly larger area of hyperknesis following the histamine-evoked itch compared with the controls. Hyperknesis and hyperalgesia are suspected to share somewhat similar mechanisms—involvement of the central sensitization. Hypersensitivity to pain has been reported in PD and a meta-analysis has provided evidence for the presence of hyperalgesia in PD patients[47]. This suggests that in PD patients a state of sensitization is present that might also explain a larger area of hyperknesis following the histamine-evoked itch. High concentrations of α-synuclein have also been observed in the skin of PD patients[22], which can explain alterations the function of sensory fibers. However, Wang et al[48] did not find evidence of α-synuclein accumulation in the sensory fibers in the skin of PD patients. Deposition of α-synuclein in the CNS is, however, a common finding in PD[49] and can influence the alterations in centrally mediated sensory information.

A potential effect of medication must also be considered in sensory responses tested in this study. It has been demonstrated that pain thresholds are lower in patients without dopaminergic drugs, but return to the normal level with levodopa treatment[11,50]. Of our PD patients, 90% were on levodopa and besides alterations that this drug can cause in sensory perception related to pain, it has been reported that levodopa can cause itching as a side effect. The effect of PD on different sensory fibers and the outcome with and without medication need further investigation.

Histamine-induced itch intensity

No significant difference was observed between the temporal profile of the histamine-induced itch between PD patients and controls. Evoked itch intensity, in terms of peak, or overall itch (AUC under itch intensity-time curve) did not yield any significant difference between PD and controls. Histamine-induced itch sensation disappears usually after 8–15 minutes[51], and we also observed that on average the itch disappeared in both groups within this time range.

Studies have reported that the prevalence of pruritus increases with age and can be partially attributed to a decline in normal physiological status of the skin[52–54]. However, this study found no correlation between age and histamine-induced itch intensity. A higher pain, however, was observed throughout the entire experiment in PD patients compared with controls, which is in line with previous reports[13,15,55,56]. Several mechanisms have been proposed to underlie the effects seen as sensory alterations related to pain in PD. For example, mitochondrial dysfunction in dopaminergic neurons in PD has been proposed to lead to hyperactivity of the nociceptors[57]. Another theory is that decreased levels of dopamine in PD might result in a lower pain threshold[9]. However, inconsistent results are present in the literature of pain in PD patients with and without levodopa treatment.

Only a few studies have explored sex differences in relation to pruritus[37,38]. Ständer et al[38] investigated 1037 patients (469 males; 568 females) with chronic pruritus and concluded that females more often reported occurrence of localized itch attacks, with stinging, warmth and painful qualities compared with the males with chronic pruritus. A study by Stumpf et al[58] (278 males; 341 females) has shown that females were more anxious than males, and that anxiety scores in females were related to the intensity of pruritus. Multiple explanations could justify the difference in itch sensations between males and females. We did not find any sex-related response, but a larger cohort is required to investigate possible sex-related differences.

Dispersion of itch in response to histamine-induced itch model

When using the histamine-evoked itch model, the sensation and dispersion of itch are expected to be centered around the application site[51], which was also the case in this study. The dispersion of itch was traced on the arm charts after the histamine-induced itch had disappeared. No significant difference was found between PD patients and controls; but the dispersion of itch was more scattered and away from the center of the histamine application area in PD patients compared with controls. Perhaps, neurodegeneration of unmyelinated fibers in PD patients could affect the itch-transmitting C-fibers[59], which could explain the difference in itch dispersion. However, lack of significant difference in finding requires future studies with application of other methods such as nerve recording or brain imaging techniques, for example, functional magnetic resonance (fMRI) could be a useful tool to detect the centers that are activated in the brain. We still do not know if a phenomenon similar to the referred pain[60] may occur in relation to itch, that is "referred itch." The scattered itch dispersion in PD patients might be explained by the appearance of referred itch potentially medicated by the central sensitization.

This pilot study is not without limitations. Other itch provocation tests (eg, nonhistaminergic provocations) could be tested with application of other methods in addition to psychophysical measurements to shed light on the mechanisms underlying sensory alterations. It has been proposed that histamine activates 2 populations of afferent fibers, one that mediates itch and alloknesis and the other that activates pain pathways and gives an antipruritic effect to itch and its associated dysesthesia[61]. How PD mechanisms can influence sensory alterations in response to itch needs further basic research[62] in line with clinical studies.

Conclusion

This study investigated the patterns and characteristics of sensory abnormalities with a focus on itch in PD patients compared with their matched controls. There was no significant difference in spontaneous or evoked itch parameters between the 2 groups, except the presence of significantly larger areas of hyperknesis in response to the histamine-induced itch model in PD patients. This finding proposes a potential alteration in central processing of itch that needs further investigation and whether and how it is affected by, for example, PD pathogenesis.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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