Dermatology Practical & Conceptual

The Prevalence and Clinical Significance of Skin Manifestations in Parkinson's Disease Patients

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ABSTRACT

Background: Parkinson's disease (PD) is primarily characterized by motor symptoms, but non-motor symptoms, including skin manifestations, are increasingly recognized. These remain underexplored despite their potential impact on quality of life.

Objectives: This study aimed to evaluate the prevalence and clinical features of skin findings in PD patients, with a focus on identifying potential pathogenetic links between dermatological conditions and PD.

Methods: A total of 215 PD patients were included. Comprehensive dermatological examinations were performed, and demographic and clinical data were collected. Statistical analysis was conducted using SPSS 23.0, with significance set at $P < 0.05$.

Results: Skin conditions were found in 92.1% of PD patients. Xerosis, seborrheic dermatitis, and hyperhidrosis were the most common findings. Pre-PD xerosis was associated with an earlier stage of PD ($P = 0.001$). Use of PD medications, such as levodopa/carbidopa/entacapone, was linked to a lower incidence of seborrheic dermatitis ($P = 0.040$). A significant correlation was also noted between rosacea and cherry angioma ($P = 0.01$).

Conclusion: Dermatological conditions are prevalent in PD and may precede its motor symptoms. Skin assessments could aid early diagnosis and management of PD, highlighting the need for further research on their pathogenetic mechanisms.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by the triad of resting tremor, bradykinesia, and rigidity. In patients with PD, mainly motor disorders are observed; however, non-motor symptoms can also be seen at all stages of the disease. The most common non-motor symptoms are pain, sweating, insomnia, depression, and skin manifestations [1-5]. These symptoms may occur before the onset or during the course of PD. Recent studies suggest a close relationship between neurological symptoms and skin findings in PD [1,2,6,7]. These studies have reported a higher incidence of seborrheic dermatitis (SD), rosacea, and sweating dysfunction in patients with PD [1–10]. In this context, there is a need for further studies on the relationship between skin diseases and PD in order to elucidate the pathogenesis of these diseases.

Nevertheless, skin problems associated with PD that worsen the quality of life of PD patients go unnoticed or are underestimated by both the patient and the doctor who follows the patient.

Objectives

In view of the foregoing, the objective of this study was to investigate the prevalence and clinical features of skin findings in PD in order to reveal the relationships, if any, between the skin and the nervous system.

Materials and Methods

Study Population

The population of this cross-sectional observational study consisted of patients who were followed up with PD diagnosis in the XXX Hospital Neurology Outpatient Clinic and for whom the XXX Dermatology Outpatient Clinic was consulted between March 2022 and March 2023.

Demographic and Clinical Characteristics

Patients' demographic and clinical characteristics, including age, sex, known dermatological diseases, PD duration, PD stage according to Hoehn & Yahr staging system (stage 1: Unilateral involvement only, usually with minimal or no functional disability; stage 2: Bilateral or midline involvement, without impairment of balance; stage 3: Bilateral disease, mild to moderate disability with impaired postural reflexes; physical independence, stage 4: Severely disabling disease, ability to walk or stand unassisted, stage 5: Confinement to bed or wheelchair unless aided), additional chronic diseases, regularly used PD medications and other regularly used medications were recorded.

Physical Examinations

Whole-body skin, scalp, nail, and oral mucosa examinations were performed on all patients, and the resulting skin findings were noted.

Pathology Investigations

It was investigated whether these pathologies started before, after, or simultaneously with PD and whether they progressed with PD.

Ethical Approval

The study protocol was approved by the XXX Hospital Ethics Committee (Approval No: E1-22-2404).

Statistical Analysis

Statistical analyses of the collected data were conducted using the SPSS 23.0 (Statistical Product and Service Solutions for Windows, Version 23.0, IBM Corp., Armonk, NY, US, 2015) software package. Percentages and proportions were used to express categorical variables, and mean (standard deviation, SD) or median (interquartile range, IQR) values were used to express numerical variables. Categorical variables were analyzed using the chi-square test, and numerical variables were analyzed using the student's t-test or Mann-Whitney U test. Probability (p) statistics of < 0.05 were deemed to indicate statistical significance.

Results

Demographic and Clinical Characteristics of Patients

The study sample consisted of 215 PD patients: 143 (66.5%) male and 72 (33.5%) female. The mean age of the sample was 65.15 ± 9.8 years. Of the PD patients followed at the neurology polyclinic and for whom dermatology outpatient clinic was consulted, skin diseases were detected in 16.3%, scalp disease in 5.1%, nail disorders in 2.8%, and no dermatological problem was detected in 75.8%. Additionally, systemic disease was detected in 43.3% of the patients. Patients' demographic and clinical characteristics are summarized in Table 1.

Findings from Dermatological Examination

Skin, scalp, nail, and oral mucosa findings obtained in dermatological examination revealed at least one skin disease in 92.1% of the patients, at least one scalp disease in 39.1%,

Table 1. Demographic and Clinical Characteristics of Patients Participating in the Study.

Sex	Frequency (%)
Female	33.5
Male	66.5
Age, *average (SD)*	65.15 (±9.8)
Reason for Attending the Dermatology Polyclinic	**Frequency (%)**
Skin disease	16.3
Scalp disease	5.1
Nail disease	2.8
No complaint	75.8
PD duration *median, years (IQR)*	4 (2-7)
PD stage	**Frequency (%)**
1	17.2
2	51.6
3	20.1
4	8.8
5	2.3
PD Treatment	**Frequency (%)**
Levodopa+DK inhibitor	73
MAO B inhibitor	83.3
Non-ergot dopamine agonist	81.4
Levodopa+DK inhibitor +COMT inhibitor	25.1
Amantadine	21.4
Levodopa/Carbidopa Intestinal Gel	5.6
Deep Brain Stimulation (DBS-Brain Stimulator)	0.9
PD Treatment Duration *median, years (IQR)*	3 (1-6)
Previously Known Dermatological Disease in the Patient	**Frequency (%)**
Yes	5.2
Seborrheic Dermatitis	3.3
Rosacea	1.4
Vitiligo	0.5
Duration median, years (IQR)	7 (5-15)
No	94.8
Systemic Disease	**Frequency (%)**
Yes	43.3
No	56.7
The Three Most Common Systemic Diseases	**Frequency (%)**
Hypertension	29.3
Diabetes mellitus type 2	19.5
Hypothyroidism	3.8

Abbreviations used in this table include SD for standard deviation, IQR for interquartile range, PD for Parkinson's disease, DK inhibitor for decarboxylase inhibitor, MAO B inhibitor for monoamine oxidase B inhibitor, COMT inhibitor for Catechol-O-methyltransferase inhibitor, and DBS for Deep Brain Stimulation. The percentages indicate the proportion of patients with each characteristic or treatment, and the median years (with IQR) reflect the duration of PD and PD treatment as well as the duration of previously known dermatological diseases, where applicable.

Table 2. Summary of Dermatological Examination of Skin, Scalp, Nail, and Oral Mucosa.

	Freq %	Duration, median *months (IQR)*	Appearance of Skin, Scalp, and Nail Mucosa Findings		
			Before PD, *Freq %*	with PD, *Freq %*	After PD, *Freq %*
Skin Findings					
Xerosis	60.9	60 (36-60)	57.3	29.7	13.0
Cherry angioma	45.1	60 (36-60)	79.3	18.6	2.1
Hyperhidrosis	37.2	48 (24-60)	56.2	26.3	17.5
Seborrheic dermatitis	27.4	48 (24-60)	66.1	28.8	5.1
Rosacea	27.4	48 (36-60)	55.9	37.3	6.8
Erythema intertrigo	16.3	4 (2-5)			
Xerotic eczema	13	60 (36-60)			
Tinea pedis	14.4	4 (2-6)			
Actinic keratosis	9.8	60 (36-60)			
Hand eczema	4.1	60 (36-60)			
Stasis dermatitis	2.3	24 (24-36)			
P versicolor	1.9	2 (2-5)			
Scalp Disease					
Seborrheic dermatitis	31.6	48 (24-60)	50.8	44.4	4.8
Actinic keratosis	11.6	36 (30-60)			
Folliculitis	4.7	12 (12-15)			
Nail Disease					
Tinea ungium	14.9				
Longitudinal ridges	9.3				
Terry's nail	1.4				
Subungual Hyperkeratosis	1.4				
Muehrcke's nails	0.9				
Oral Mucosa					
Atrophic glossitis	0.9				
Black tongue	0.5				

This table presents the findings from dermatological examinations focusing on skin, scalp, nail, and oral mucosa conditions in Parkinson's disease (PD) patients. "Freq %" indicates the percentage of patients exhibiting each condition. "Duration, median months (IQR)" provides the median duration of each condition in months, along with the interquartile range (IQR), reflecting variability among patients. "Before PD", "With PD", and "After PD" percentages denote the timing of onset of each condition relative to the diagnosis of PD. Conditions without specified percentages for "Before PD", "with PD", and "After PD" did not have sufficient data for these categories. "Tinea ungium", "Longitudinal ridges", "Terry's nail", "Subungual hyperkeratosis", and "Muehrcke's nails" under Nail Disease as well as "Atrophic glossitis" and "Black tongue" under Oral Mucosa are reported without specific frequency or timing related to PD due to the nature of these findings.

nail disease in 27.4%, and oral mucosa disease in 1.4%. Skin, scalp, nail, and oral mucosa findings obtained in dermatological examination are summarized in Table 2.

Association between Pre-PD Dermatological Conditions and PD Stage

In patients with pre-PD xerosis, the PD stage was earlier (stage 1: 22.8%, stage 2: 54.3%, stage 3: 17.4%, stage 4: 4.1%, and stage 5: 1.4%) than in patients without pre-PD xerosis (stage 1: 7.2%, stage 2: 44.7%, stage 3: 34,1%, stage 4: 12.5%, and stage 5: 1.5%) (p=0.001) (Table 3).

Dopalevo use was significantly lower in patients with pre-PD xerosis than in those without pre-PD xerosis (14.7% vs. 39.3%, $P = 0.028$).

The rate of PD patients with SD on the face and body was significantly higher among male patients than female patients (35% vs. 12.5%, $P < 0.001$). SD was significantly less common among those using levodopa/carbidopa/entacapone ($P = 0.040$). SD was also significantly less common in patients who had been using dopa agonists than in patients who had not been using dopa agonists (24.6% vs. 40%, $P = 0.049$). Pre-PD SD was significantly more common

Table 3. Comparative Analysis of Dermatological Conditions across Parkinson's Disease Stages.

PD Stage	Xerosis, Freq %			SD, Freq %			SSD, Freq %			Rosacea, Freq %			Hyperhidrosis, Freq %		
	pos	neg	P	pos	neg	P	pos	neg	P	pos	neg	P	pos	neg	P
1	22.8	7.2	0.001	22.2	16.2	0.011	28.1	3.2	<0.001	16.6	21.1	0.67	14.3	29.5	0.096
2	54.3	44.7		66.7	48.6		59.4	41.9		50.5	57.6		51.4	40.9	
3	17.4	34,1		8.3	22.3		9.4	35.5		20.9	15.2		14.3	25	
4	4.1	12.5		2.8	10.1		3.1	12.9		9.3	6.1		14.3	2.3	
5	1.4	1.5		0	2.8		0	6.5		2.7	0		5.7	2.3	

This table presents a comparative analysis of the frequency percentages of various dermatological conditions across different stages of Parkinson's Disease (PD), ranging from stage 1 to stage 5 according to the Hoehn and Yahr scale. "Freq %" columns under each condition (Xerosis, Seborrheic dermatitis (SD), Scalp seborrheic dermatitis (SSD), Rosacea, and Hyperhidrosis) are divided into "pos" for positive (presence of the condition) and "neg" for negative (absence of the condition), indicating the proportion of patients at each PD stage. P-values indicate the statistical significance of the differences observed between the presence and absence of each condition at various PD stages, with values less than 0.05 considered statistically significant. The absence of a p-value indicates that statistical analysis data for those stages are not provided. This analysis aimed to identify potential correlations between the progression of PD and the prevalence of specific dermatological conditions. Chi-squared test.

in male patients than in female patients (21% vs. 8.3%, $P = 0.019$). The PD stage at admission to our outpatient clinic was significantly lower in patients with pre-PD SD than in patients without pre-PD SD (stage 1: 22.2% vs. 16.2%, stage 2: 66.7% vs. 48.6%, stage 3: 8.3% vs. 22.3, stage 4: 2.8% vs. 10.1%, and stage 5: 0% vs. 2.8%; $P = 0.011$) (Table 3).

Specific Dermatological Conditions in PD Patients

Cherry angioma (25 <) was significantly more common in PD patients with rosacea than in PD patients without rosacea (59.3% vs. 40.3%, $P = 0.01$). In parallel, rosacea was significantly more common in PD patients with cherry angioma than in PD patients without cherry angioma (36.1% vs. 20.3%, $P = 0.01$). Erythema intertrigo and tinea pedis were significantly more common in PD patients with hyperhidrosis than in PD patients without hyperhidrosis ($P < 0.001$). The PD stage at admission to our outpatient clinic was significantly lower in patients with pre-PD SD on the scalp than in patients without pre-PD SD on the scalp (stage 1: 28.1% vs. 3.2%, stage 2: 59.4% vs. 41.9%, stage 3: 9.4% vs. 35.5%, stage 4: 3.1% vs. 12.9%, stage 5: 0% vs. 6.5%; $P < 0.001$) (Table3).

Actinic keratosis was observed on the face of 9.8% of the PD patients and on the scalp of 4.7%.

In patients with additional systemic diseases other than PD and drug use other than PD, there was no statistically significant relationship between skin findings ($P > 0.05$)

Improvement of Dermatological Findings After PD Diagnosis

Of the patients with pre-PD dermatological findings, 92.4% described improvement in these findings after PD. In cases with skin findings detected after dermatological examination, the patients noticed the findings in 62.6% of the cases and the neurologist in 4.5%.

Conclusions

PD, which affects approximately 0.3% of the general population, is a disease that progresses with the loss of dopaminergic neurons in the substantia nigra [1,3,5,11]. The incidence of PD, which is more common in men, increases after the fifth decade [2]. Although the pathogenesis of PD is not fully known, it has been suggested that factors such as mitochondrial dysfunction, oxidative stress, immune dysregulation, and chronic inflammation may lead to PD [1].

Despite the general view that PD cases are sporadic, it has been reported that mutations detected in the Parkin (PARK2), PINK1 (PARK6), LRRK2, PARK7, and SNACA genes may be associated with PD [1,2,12].

PD is a hypokinetic motor disorder; however, non-motor symptoms can also be observed at all stages of the disease. Recent studies have suggested that the skin is an organ where non-motor symptoms are frequently observed [1,2].

PD is classified as a synucleinopathy due to the pathological accumulation of alpha-synuclein and the formation of Lewy bodies and Lewy neurites [1,4,6,11,13]. It has been shown that alpha-synuclein, a small protein consisting of 140 amino acids, plays a role in some cellular mechanisms, suggesting that its accumulation in peripheral tissues and the brain causes non-motor symptoms in PD, including in the skin [1,6,7,14].

In 2008, Ikemura et al. detected alpha-synuclein deposits in the skin samples taken from the abdominal wall and upper extremities of 279 PD patients who had undergone autopsy. They also detected localized alpha-synuclein immunoreactivity in the dermis in 23.5% of the patients with Lewy pathology in the central nervous system [15].

In comparison, in our study, 75.8% of the PD patients had no dermatological complaint. However, dermatological examination revealed at least one skin disease in 92.1% of the patients, at least one scalp disease in 39.1%, nail disease in 27.4%, and oral mucosa disease in 1.4%.

The most common skin finding in our study was xerosis, common in the geriatric population. The frequent occurrence of xerosis in PD patients may be due to age or autonomic dysfunction. In our study, in most PD patients with xerosis, xerosis occurred before PD. Therefore, we think xerosis may be a non-motor precursor skin lesion associated with PD. Additionally, the PD stage at admission to our outpatient clinic was significantly lower in patients with xerosis than those without xerosis, suggesting that xerosis is a good prognostic factor. A thorough literature review did not reveal any study on xerosis in patients with PD.

Dyshidrosis (hyperhidrosis and hypohidrosis), which is considered a part of orthostatic dysfunction, is a common finding in PD. In our study, hyperhidrosis was observed in 37.2% of the patients. Pont-Sunyer et al. reported that patients with PD had excessive sweating for 2–10 years before the onset of typical motor symptoms [16]. Similarly, complaints of the majority of PD patients with hyperhidrosis in our study had started before the diagnosis of PD. Wamelan et al. reported that chronic hyperhidrosis may be associated with the dysautonomic dominant subtype of PD and can thus be used as a simple clinical screening tool. It has been suggested that sweating in PD patients occurs mainly in the head and trunk as part of a compensatory thermoregulation mechanism against the loss of sweating in the extremities [9].

In our study, we detected hyperhidrosis more frequently in female PD patients. In contrast, Wamelan et al. did not report any significant difference in the rate of hyperhidrosis according to sex [9].

In our study, we detected SD in 31.6% of patients with PD on the scalp and 27.4% in the skin on the face other than the scalp and the skin on the chest and/or other body parts.

Our finding that the rate of SD, which is seen at 1-3% in the general population, was higher in PD patients is consistent with other studies conducted to date [1,2]. Krestin et al. reported seborrheic face as a skin finding in PD patients in 1927 [1,7]. In a retrospective study, Tanner et al. suggested that SD may be an early marker of PD [1].

In PD, dopamine deficiency causes a deficiency of melanocyte-stimulating hormone (MSH) inhibitory factor, causing an increase in alpha-MSH and sebum production. In addition, decreased facial mobility in PD contributes to a greater accumulation of sebum. Mortignoni et al. found SD to be more common in male PD patients [17]. Arsenijevic et al. found a positive correlation between SD, PD, Malassezia globosa incidence, high yeast density, and high skin phosphatase and lipase activity [18]. Additionally, numerous alpha-synuclein aggregates have been found in the sebaceous glands in skin biopsies of patients with PD [14]. Alpha-synuclein deposits may affect sebum production and excretion in the sebaceous glands, causing skin oiliness or dryness.

In our study, the frequency of SD in patients using levodopa/carbidopa/entacapone and dopa agonists was statistically lower than in patients not using these drugs. Kohn et al. found a significant decrease in the sebum on the foreheads of patients receiving L-dopa treatment. They did not find a relationship between dopa dose, treatment duration, and degree of sebaceous gland inhibition [19]. Martignoni et al. found no correlation between sebum excretion rates and duration of L-dopa treatment [17]. Tomic et al. found a positive correlation between age, motor symptom severity, and SD in PD [4]. In contrast, we did not find any significant relationship between PD stage, age, and SD. Tomic et al. found that 1/3 of the patients had symptoms of SD before PD diagnosis, and SD was 1.8 times more common in patients with moderate and severe symptoms than in patients with mild symptoms [4]. In our study, 61% of the PD patients had SD before they were diagnosed with PD. Unlike Tomic et al., we found the PD stage at admission to our outpatient clinic to be significantly lower in PD patients with SD than in those without SD. These findings suggest that PD may be less severe in patients with SD. Rosacea, whose prevalence in the population varies between 1% and 20% [1], was observed at a high rate in patients with PD in our study. A few studies suggested a relationship between rosacea and PD [8,20,21]. The relationship between PD and rosacea is not fully known. However, common mechanisms involving increased matrix metalloproteinase (MMP) activity have been suggested to play a role in the relationship between PD and rosacea. In addition, it has been stated that increased levels of MMP-3 and MMP-9 in the cerebrospinal fluid may lead to the death of dopaminergic neurons, and simultaneously, increased levels of MMP-1, MMP-3, and MMP-9 in the skin may lead to tissue damage [1,2,8]. Additionally, sensory nerve fiber dysfunction is thought to cause immune destabilization and opportunistic skin diseases in sensitive areas of the skin [1,8].

PD also affects the entire gastrointestinal system. Bacterial overgrowth in the small intestine and H. Pylori may contribute to the pathogenesis of rosacea [1,2,22]. We found cherry angioma to be more common in patients with rosacea and rosacea to be more common in patients with cherry angioma. A thorough literature review did not reveal any study touching on that relationship. The fact that both diseases were seen more frequently together may be attributed to their similar pathogenesis.

The prevalence of actinic keratosis (AK) varies from country to country, e.g., Italy: 1.4%, South Korea: 88% [23]. In a study conducted in Turkey, Yaldız et al. reported the prevalence of AK as 4.61% between the ages of 60 and 69,

9.38% between the ages of 70 and 79, and 14.5% above the age of 80 [24].We did not observe an increase in the incidence of AK in PD patients. There are conflicting results in the literature regarding the relationship between precancerous skin lesions and malignancies in PD [12,23]. Ferreria et al. reported an increase in the risk of skin cancer with PD [23]. In a meta-analysis study, Zhang et al. reported an inverse relationship between PD and total cancer risk, except for melanoma [12]. This finding may be explained by genes associated with PD. PARK2 is a tumor suppressor gene, while LRRK2 mutations are associated with an increased risk of cancer [12]. We did not detect skin cancer in patients with PD in our study.

Similarly, we did not detect a significant increase in nail and oral mucosal diseases in patients with PD. The most common nail disease in patients with PD was onychomycosis.

The examining neurologist detected only 4.5% of the skin findings in PD patients, indicating that the skin findings of the PD patients were ignored by both the patient and the neurologist.

This study investigated the skin findings in patients with PD. Consequently, xerosis, hyperhidrosis, seborrheic dermatitis, rosacea, and cherry angioma were found to be common in patients with PD. On the other hand, premalignant skin lesions were rarely observed in these patients. The PD stage was mostly lower in patients with xerosis and pre-PD SD. These findings suggest that xerosis and SD can be used as effective prognostic markers in PD. However, further large-scale studies are needed to corroborate the findings of this study.

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