Review Article

A review of the gastrointestinal, olfactory, and skin abnormalities in patients with Parkinson's disease

Mohannad A. Almikhlafi, *Pharm.D., Ph.D.*

ABSTRACT

مرض باركنسون هو اضطراب حركي عصبي تنكسي معقد يسبب فقدان الخلايا العصبية الدوبامينيرجية في نواة سوداء متراكبة. النواة السوداء ليست المنطقة الدماغية الوحيدة التي تتأثر بواسطة هذا الاضطراب وليست الأولى. أظهرت الدراسات الحديثة والقديمة أن هذا الاضطراب لا يؤثر فقط على الجهاز العصبي المركزي. في الواقع، تم العثور على تأثير ترسيب الألفا–سينوكلين في الترويع الذاتي للجهاز الهضمي، والجلد، والجهاز الشمي خارج الجهاز العصبي المركزي، مما يؤثر على جودة حياة المرضى. في الجهاز الهضمي، تعتبر صعوبة البلع والإمساك وتكاثر البكتيريا في الأمعاء الدقيقة شائعة لدى المرضى. بالإضافة إلى ذلك، تم الإبلاغ عن حالات عدة من الأمراض الجلدية في الحالات، بما في ذلك التهاب الجلد الدهني، والوردية، وسرطان الجلد، وغيرها. وأخيراً، كانت تشوهات الجهاز الشمي، مثل انخفاض الحس بالملمس والشم، مرتبطة بالشذوذات الحركية. هناك حاجة إلى دراسات عالية الجودة إضافية لتطوير اختبارات موثوقة يمكن أن تساعد في التشخيص في وقت مبكر.

Parkinson's disease (PD) is a complex neurodegenerative motor disorder caused by the loss of dopaminergic neurons in the substantia nigra pars compacta. The substantia nigra is neither the first nor the only brain region affected by PD. Recent and old studies have shown that PD does not only affect the CNS; in fact, autonomic innervation in the GIT, skin, and olfactory system was found to be affected by α-synuclein pathology outside the CNS, affecting patients' quality of life. In the gastrointestinal system, dysphagia, constipation, and bacterial overgrowth in the small intestine are common in patients with PD. In addition, several skin conditions were reported in PD, including seborrheic dermatitis, rosacea, melanoma, and others. Finally, olfactory system dysfunction, such as reduced touch sensation and smell, was associated with motor abnormalities. Further high-quality studies are needed to develop reliable tests that could help in the early diagnosis of PD.

Neurosciences 2024; Vol. 29 (1): 4-9
doi: 10.17712/nsj.2024.1.20230062

From the Department of Pharmacology and Toxicology, Taibah University, Madinah, Kingdom of Saudi Arabia

Address correspondence and reprint request to: Dr. Mohannad A. Almikhlafi, Department of Pharmacology and Toxicology, Taibah University, Madinah, Kingdom of Saudi Arabia.
E-mail: Mmikhlafi@Taibahu.edu.sa
ORCID ID: https://orcid.org/0000-0002-4499-8605

Parkinson's disease (PD) is the second most common disorder of the central nervous system; it results in the progressive death of dopaminergic neurons in the brain.[1] This neurodegenerative disease is projected to affect approximately 6 million people worldwide.[2] People with PD experience neurodegeneration in the brain as well as the peripheral autonomic nervous system, which maintains involuntary processes such as heart rate, blood pressure, respiration, digestion, and sexual arousal.[3] Patients with PD experience a variety of gastrointestinal (GI) tract abnormalities, but the cause of these symptoms remains unclear.[4] The GI disorders such as dysphagia (difficulty or discomfort swallowing), gastroparesis (paralysis of the stomach), and bowel dysfunction (constipation) are among the most prevalent non-motor symptoms of PD.[5] Moreover, the association between PD and the olfactory system (OS) and skin disorders has been used as a biomarker in the diagnosis of PD.[6] Therefore, early PD pathology can be diagnosed not only by motor symptoms, but also by skin and OS abnormalities.[7] Researchers have indicated that aging is responsible for hyposmia, or the reduced sense of smell, in patients with PD.[8] This article aims to discuss PD beyond the brain, with a focus on the role of alpha-synuclein pathology in the GI tract, the OS, and skin disorders.

Gastrointestinal system. The GI abnormalities and symptoms are frequently present in patients with PD, but the extent of GI dysfunction in the development of PD remains unclear.[9] The GI function is controlled by the enteric and autonomic nervous system. Enteric nervous system consists of distinct types of neurons and glial cells that can be found in the esophageal, gastric, and intestinal tissues. Input from the autonomic nervous system to the enteric nervous system is essential for gastric and intestinal function. In PD, it has been found that patients with PD have more localization of Lewy bodies enteric nervous system than healthy control. Also, PD patients were determined to have fewer dopaminergic

neurons in the colonic enteric nervous system as well as low level of dopamine in the muscularis externa. All these changes are responsible for the non-motor symptoms in PD.

In recent years, researchers have highlighted GI dysfunction in patients with PD, including dysphagia, gastroparesis, also known as delayed gastric emptying, and bowel disorder (**Table 1**) (**Figure 1**).[10] More recently, GI abnormalities have been identified as contributing to the development of depression in patients with PD. The GI dysfunction in these patients leads to progressive disorders and a significant reduction in quality of life.[11]

Dysphagia. Upper GI tract complaints, such as dysphagia, are present in 9%–77% of patients with PD, with a clear tendency to increase in frequency and severity as the population ages. Dysphagia is more closely associated with a substantial fatality rate due to malnutrition and pulmonary disorders. This symptom occurs mostly in patients who are in the late stages of PD. The exact mechanism of oropharyngeal dysphagia in PD is still not well defined.[12] A meta-analysis was conducted to estimate the severity and prevalence of dysphasia in patients with PD in different counties. The authors included 20,530 patients with PD from 58 studies. The estimated pooled prevalence of dysphagia in patients with PD was 36.9% (95% CI 30.7%–43.6%). Instrumental assessment indicated a higher prevalence rate of 57.3% (95% CI 44.3%–69.1%). Oceania exhibited the highest prevalence and severity of dysphagia followed by Africa, Asia, Europe, and America.[13]

Small intestinal bacterial overgrowth. Patients with PD also experience small intestinal bacterial overgrowth (SIBO), which results in the production of tyrosine decarboxylate.[14] The prevalence of SIBO in patients with PD has been estimated at 25–55%. A variety of gut microbes have been identified in various studies in patients with PD, and these bacterial species are implicated in GI disorders.[15] Here, we describe a mechanism by which the efficacy of levodopa, which is used as a dopamine replacement agent for the treatment of PD, is reduced by changes in the composition of the gut microbiome. The first stage is associated with intestinal dysfunction resulting in secondary bacterial overgrowth. In this mechanism, tyrosine decarboxylase produced by certain types of bacteria in the gut is also involved in the decarboxylation of levodopa, which reduces its efficacy in patients with PD. Tyrosine decarboxylase blocks the circulation of dopamine in the brain.[16]

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Constipation. Constipation is one of the main non-motor symptoms of the lower GI tract in patients with PD: It occurs when bowel motility is reduced, and stool passage becomes difficult.[17] Constipation may even precede motor symptoms due to early alpha-synuclein pathology of the enteric nervous system and vagus nuclei.[18] A study was conducted to examine the relationship between constipation and the progression of PD. The pooled odds ratio for constipation was 2.27 (95% CI 2.09–2.46) in patients with PD compared with healthy controls. Therefore, this meta-analysis suggests that constipation may trigger and increase the progression of PD compared with a healthy individual.[19] Another study was conducted to examine the prevalence of GI symptoms among 103 patients with PD and 81 healthy individuals. The participants were given a questionnaire that included questions about GI symptoms such as constipation, indigestion, dysphagia, diarrhea, nausea, vomiting, bloating, and abdominal pain. The authors concluded that the risk of constipation was higher in people with PD (78.6%) compared with healthy individuals (28.4%). Many people with PD also complain of other GI symptoms.[20-24]

In conclusion, patients with PD commonly experience various GI tract symptoms. However, the available meta-analyses and systematic research, based on questionnaires, are insufficient to assess disease severity and prevalence. Early screening for GI abnormalities in PD could prevent or mitigate the complications by early intervention. In addition, more research is needed to better understand the connection between PD and GI abnormalities, thus discovering better therapeutic strategies.

Olfactory system. While PD is commonly linked with motor symptoms, numerous studies have shown that along with various other non-motor symptoms, olfactory dysfunction emerges as a particularly crucial feature for PD diagnosis, being present in approximately 96% of PD patients.[25] The OS is the sensory system that is crucial for the sense of smell in humans.[26] The initial symptoms of olfactory dysfunction are often sensory and include a reduced sense of touch and smell.[27,28] Hyposmia (loss of the sense of smell) is one of the most important symptoms for early detection of PD.[29] The exact mechanism responsible for OS impairment in patients with PD is still unknown. However, there are various factors that are involved in the pathology of OS disorders. As described by Braak staging, a method used to categorize the degree of pathology in PD, LB pathology originating in the olfactory bulb

Table 1 - Most common Parkinson's disease-associated GI disorders.

Symptoms	Prevalence	References
Dysphagia (difficulty or discomfort in swallowing)	9%–77%	(12)
Gastroparesis (paralysis of the stomach)	~45%	(21) (22)
Bowl disorder (Constipation)	61% in PD patients and 24.5% had constipation before the appetence of the motor symptoms	(23, 24)
Small intestinal bacterial overgrowth (SIBO)	25%–55%.	(15)

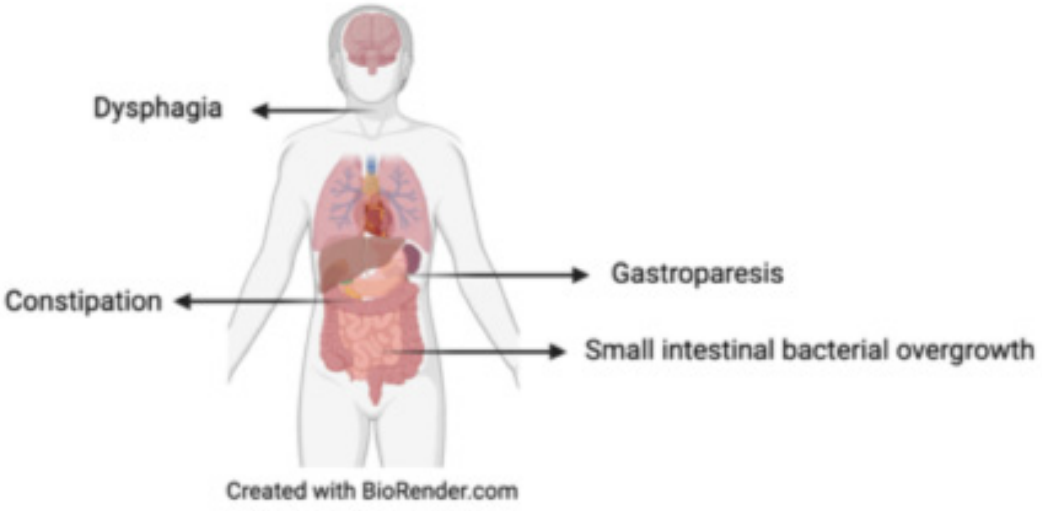

Figure 1 - Association between Parkinson's disease and gastrointestinal dysfunctions.

and the dorsal nucleus of the vagus nerve corresponds to the early pathology of OS dysfunction.[30] Autopsy revealed an early deposition of alpha-synuclein in the entorhinal cortex, the central nucleus of the amygdala, the piriform cortex, and the anterior olfactory cortex, which might be responsible for this symptom.[31,32] Another factor implicated in OS impairment is changes in neurotransmitter (i.e., dopamine, acetylcholine, and serotonin) levels.[33]

Prevalence of olfactory system dysfunction and act as a biomarker in PD. A meta-study was conducted to estimate the prevalence of OS impairment in patients with PD in Europe and Australia. Among the 400 patients with PD, 51.7% had hyposmia, 45.0% had anosmia (partial or complete loss of smell), and 3.3% had a normal sense of smell.[34] Haehner et al[35] evaluated 474 patients with OS dysfunction, and 9.8% of patients were diagnosed with PD after a few years, suggesting that OS dysfunction may be an early sign of PD.

A meta-analysis was conducted to explore the prevalence of hyposmia in patients with PD. The authors collected data from various databases such as the Cochrane Library and PubMed. They used the Newcastle–Ottawa Scale and a pooled analysis (i.e., statistical methods used when pooling and evaluating the results of multiple epidemiological studies) in their assessment. There were 3272 patients with symptoms of hyposmia and 176 patients with PD with 3–17 years of follow-up. The pooled odds ratio for hyposmia in patients with PD was 3.84 (95% CI 2.12–6.95). The result of this meta-analysis suggest that OS impairment is directly involved in the pathogenesis of PD.[36]

In another study, the authors aimed to explore the relationship between cognition, anxiety, and OS impairment with disease severity in PD. They divided 105 patients with PD into 2 groups: those with anosmia and those with normal smell. The authors used the University of Pennsylvania Smell Identification Test (UPSIT), a commercially available test that involves identifying odors to assess the functioning of an individual's OS; the Unified PD Rating Scale (UPDRS), an evaluation tool used to evaluate the severity and progression of PD; and the Beck Depression Inventory (BDI-II), a 21-item self-report inventory designed to

Table 2 - Types of skin manifestations and their clinical implications.

Types of skin disorders	Prevalence	Location	Possible clinical treatments	References
Seborrheic dermatitis	18.6%–59%	It is mainly located in areas rich in sebum, such as the scalp, face, upper chest, and skin layer under the arms and legs.	Topical therapy: - Ketoconazole shampoo - Topical immune suppressants Systemic therapy: - Metronidazole	(48)
Rosacea	18.8%	cheeks, nose, chin, forehead, or eyelids.	- Topical and systemic (non-immunosuppressive) therapies. - Device/surgery-based therapies.	(39, 49)
Sweating disorders	hyperhidrosis 38% hypohidrosis 15%	Affects the palms, soles, underarms, and sometimes the face.	Increase sweating can be treated with: - Dopaminergic therapy - Reduction of the (OFF time) period - Long-term subcutaneous apomorphine - Intrajejunal levodopa infusion - Intradermal injection of botulinum toxin.	(50)
Bullous pemphigoid	2.3%–17.9%	Affects the lower abdomen, upper thighs, or armpits.	- Topical corticosteroids or oral doxycycline. - Systemic corticosteroids alone or in combination with adjunctive immune-suppressing or modulating therapies.	(41)

assess the presence and severity of depressive symptoms. Based on the BDI-II and UPSIT scores, the odds ratios of developing anosmia with cognitive dysfunction and depression were 2.74 (95% CI 1.01—7.46) and 2.58 (95% CI 1.06—6.29), respectively. Based on the UPDRS scores, the odds ratio for anosmia was 12.26 (95% CI 5.69–18.82). The results indicate that an increased severity of OS impairment in patients with PD leads to cognitive dysfunction and increases the pathogenesis of PD.[37]

Skin disorders in PD. As PD progresses, it is common to experience changes in skin. Skin changes such as melanoma (a form of skin cancer), excessive sweating, seborrheic dermatitis (a common form of eczema that usually affects the scalp), and rosacea (a long-term inflammatory skin condition that causes the skin to become red and itchy, usually on the nose and cheeks) are common symptoms of PD (**Table 2**).[38] Recent studies have shown an increased prevalence of skin cancer among people with PD. Research in the field of dermatology can help us understand the physiological processes that cause this common disorder. Skin manifestations have long been examined as markers of PD, and collective studies show an enhanced prevalence of various dermatological disorders in PD.[39] Seborrheic dermatitis is recognized as a premotor characteristic of PD that indicates autonomic nervous system dysregulation.[40] It should be noted that early diagnosis of PD can be detected not only by changes in the structure of the brain, but also by changes outside nervous tissues. Consistently, high concentrations of alpha-synuclein have been identified in the skin of patients with PD.[41]

The relationship and exact mechanism between melanoma and PD are still unknown. A large study was conducted to explore the association between melanoma and PD, including 2,106 patients from North American countries. The prevalence of melanoma in patients with PD was 2 times higher than in healthy controls.[42]

Sweating dysfunction is also a common symptom in patients with PD. Studies have indicated that about 38% of patients with PD complained of hyperhidrosis (increased sweating) and 15% of patients with PD had hypohydrosis (decreased sweating).[43] In a Spanish case-control study, 56 patients with bullous pemphigoid and 112 healthy people were examined. The authors concluded that the prevalence of bullous pemphigoid was 17.9% in patients with PD and 3.6% in healthy people.[44]

As mentioned above, alpha-synuclein is abundant in the central nervous as well as the peripheral autonomic nervous system. Biomarkers that allow accurate detection of dysfunctional alpha-synuclein metabolism have been discovered in the peripheral nervous system and the skin.[45] In one study, researchers evaluated the presence of alpha-synuclein in the skin of 17 healthy individuals and 17 patients with PD. Patients with PD had substantially more alpha-synuclein than healthy individuals.[46]

In one study, seborrheic dermatitis and hyperhidrosis were evaluated in 70 patients with PD and 22 healthy controls. Overall, 18.6% of patients had forehead seborrhea (excessive secretion of sebum from the sebaceous glands), and 51.4% showed normal sebum values after using non-invasive bioengineering

methods. Hyperhidrosis was found in 36 patients and they had a lower pH on their foreheads than healthy controls. Seborrhea is uncommon in treated patients, but hyperhidrosis is commonly present in patients with PD.[47-50]

Conclusion. Parkinson's disease is a complex neurological disorder that involves an interplay between central and autonomic nervous system. Motor symptoms are well known and well characterized in PD, however, non-motor symptoms often preceding diagnosis. Gastrointestinal abnormalities, notably dysphagia, constipation, bloating, and small intestinal bacterial overgrowth. Olfactory dysfunction emerges as a crucial feature for PD diagnosis, while skin disorders such as melanoma, excessive sweating, seborrheic dermatitis, and rosacea are common symptoms. A better understanding of non-motor symptoms in PD may lead to new diagnostic tools and therapeutic strategies.

References

1. Almikhlafi MA, Karami MM, Jana A, Alqurashi TM, Majrashi M, Alghamdi BS, et al. Mitochondrial Medicine: A Promising Therapeutic Option Against Various Neurodegenerative Disorders. ***Curr Neuropharmacol*** 2022.
2. Han MN, Finkelstein DI, McQuade RM, Diwakarla S. Gastrointestinal Dysfunction in Parkinson's Disease: Current and Potential Therapeutics. ***J Pers Med*** 2022; 12:
3. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. ***Parkinsonism Relat Disord*** 2011; 17: 10-15.
4. Lubomski M, Rushworth RL, Tisch S. Hospitalisation and comorbidities in Parkinson's disease: a large Australian retrospective study. ***J Neurol Neurosurg Psychiatry*** 2015; 86: 324-330.
5. Navarre CB, Pugh D. Diseases of the gastrointestinal system. ***Sheep & Goat Medicine*** 2002: 69-105.
6. Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F. Allergy and the gastrointestinal system. ***Clin Exp Immunol.*** 2008; 153: 3-6.
7. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. ***Nat Rev Drug Discov*** 2004; 3: 205-214.
8. Hansson O. Biomarkers for neurodegenerative diseases. ***Nat Med*** 2021; 27: 954-963.
9. Makaroff L, Gunn A, Gervasoni C, Richy F. Gastrointestinal disorders in Parkinson's disease: prevalence and health outcomes in a US claims database. ***J Parkinsons Dis*** 2011; 1: 65-74.
10. Klingelhoefer L, Reichmann H. The Gut and Nonmotor Symptoms in Parkinson's Disease. ***Int Rev Neurobiol*** 2017; 134: 787-809.
11. Bu LL, Huang KX, Zheng DZ, Lin DY, Chen Y, Jing XN, et al. Alpha-Synuclein Accumulation and Its Phosphorylation in the Enteric Nervous System of Patients Without Neurodegeneration: An Explorative Study. ***Front Aging Neurosci*** 2020; 12: 575481.
12. Edwards LL, Quigley EM, Harned RK, Hofman R, Pfeiffer RF. Characterization of swallowing and defecation in Parkinson's disease. ***Am J Gastroenterol*** 1994; 89: 15-25.
13. Gong S, Gao Y, Liu J, Li J, Tang X, Ran Q, et al. The prevalence and associated factors of dysphagia in Parkinson's disease: A systematic review and meta-analysis. ***Front Neurol*** 2022; 13: 1000527.
14. Fasano A, Bove F, Gabrielli M, Petracca M, Zocco MA, Ragazzoni E, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. ***Mov Disord*** 2013; 28: 1241-1249.
15. Gabrielli M, Bonazzi P, Scarpellini E, Bendia E, Lauritano EC, Fasano A, et al. Prevalence of small intestinal bacterial overgrowth in Parkinson's disease. ***Mov Disord*** 2011; 26: 889-892.
16. Beckers M, Bloem BR, Verbeek MM. Mechanisms of peripheral levodopa resistance in Parkinson's disease. ***NPJ Parkinsons Dis*** 2022; 8: 56.
17. Knudsen K, Szwebs M, Hansen AK, Borghammer P. Gastric emptying in Parkinson's disease - A mini-review. ***Parkinsonism Relat Disord*** 2018; 55: 18-25.
18. Yao L, Liang W, Chen J, Wang Q, Huang X. Constipation in Parkinson's Disease: A Systematic Review and Meta-Analysis. ***Eur Neurol*** 2023; 86: 34-44.
19. Adams-Carr KL, Bestwick JP, Shribman S, Lees A, Schrag A, Noyce AJ. Constipation preceding Parkinson's disease: a systematic review and meta-analysis. ***J Neurol Neurosurg Psychiatry*** 2016; 87: 710-716.
20. Mathers SE, Kempster PA, Swash M, Lees AJ. Constipation and paradoxical puborectalis contraction in anismus and Parkinson's disease: a dystonic phenomenon? ***J Neurol Neurosurg Psychiatry*** 1988; 51: 1503-1507.
21. Ishii T, Kinoshita KI, Muroi Y. Serotonin 5-HT(4) Receptor Agonists Improve Facilitation of Contextual Fear Extinction in an MPTP-Induced Mouse Model of Parkinson's Disease. ***Int J Mol Sci*** 2019; 20: 5340
22. Freitas ME, Alqaraawi A, Lang AE, Liu LWC. Linaclotide and Prucalopride for Management of Constipation in Patients with Parkinsonism. ***Mov Disord Clin Pract*** 2018; 5: 218-220.
23. Singer C, Weiner WJ, Sanchez-Ramos JR. Autonomic dysfunction in men with Parkinson's disease. ***Eur Neurol*** 1992; 32: 134-140.
24. Benayoun L, Pretolani M. [Airway remodeling in asthma: mechanisms and therapeutic perspectives]. ***Med Sci (Paris)*** 2003; 19: 319-326.
25. Alonso CCG, Silva FG, Costa LOP, Freitas S. Smell tests can discriminate Parkinson's disease patients from healthy individuals: A meta-analysis. ***Clin Neurol Neurosurg.*** 2021; 211: 107024.
26. Janssen Daalen JM, Tosserams A, Mahlknecht P, Seppi K, Bloem BR, Darweesh SKL. Towards subgroup-specific risk estimates: A meta-analysis of longitudinal studies on olfactory dysfunction and risk of Parkinson's disease. ***Parkinsonism Relat Disord*** 2021; 84: 155-163.
27. Kesayan T, Lamb DG, Falchook AD, Williamson JB, Salazar L, Malaty IA, et al. Abnormal tactile pressure perception in Parkinson's disease. ***J Clin Exp Neuropsychol*** 2015; 37: 808-815.
28. Oppo V, Melis M, Melis M, Tomassini Barbarossa I, Cossu G. "Smelling and Tasting" Parkinson's Disease: Using Senses to Improve the Knowledge of the Disease. ***Front Aging Neurosci*** 2020; 12: 43.
29. Lyu Z, Zheng S, Zhang X, Mai Y, Pan J, Hummel T, et al. Olfactory impairment as an early marker of Parkinson's disease in REM sleep behaviour disorder: a systematic review and meta-analysis. ***J Neurol Neurosurg Psychiatry*** 2021; 92: 271-281.

30. Silva MME, Viveiros CP, Kotsifas NJE, Duarte A, Dib E, Mercer PBS, et al. Olfactory impairment in frontotemporal dementia: A systematic review and meta-analysis. ***Dement Neuropsychol*** 2019; 13: 154-161.
31. Tarakad A, Jankovic J. Anosmia and Ageusia in Parkinson's Disease. ***Int Rev Neurobiol*** 2017; 133: 541-556.
32. Alonso CCG, Silva FG, Costa LOP, Freitas S. Smell tests to distinguish Parkinson's disease from other neurological disorders: a systematic review and meta-analysis. ***Expert Rev Neurother*** 2021; 21: 365-379.
33. Li J, Gu CZ, Su JB, Zhu LH, Zhou Y, Huang HY, et al. Changes in Olfactory Bulb Volume in Parkinson's Disease: A Systematic Review and Meta-Analysis. ***PLoS One*** 2016; 11: e0149286.
34. Rahayel S, Frasnelli J, Joubert S. The effect of Alzheimer's disease and Parkinson's disease on olfaction: a meta-analysis. ***Behav Brain Res*** 2012; 231: 60-74.
35. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. ***Rhinology*** 2017; 55: 17-26.
36. Sui X, Zhou C, Li J, Chen L, Yang X, Li F. Hyposmia as a Predictive Marker of Parkinson's Disease: A Systematic Review and Meta-Analysis. ***Biomed Res Int*** 2019; 2019: 3753786.
37. Fang TC, Chang MH, Yang CP, Chen YH, Lin CH. The Association of Olfactory Dysfunction With Depression, Cognition, and Disease Severity in Parkinson's Disease. ***Front Neurol*** 2021; 12: 779712.
38. Dabby R, Djaldetti R, Shahmurov M, Treves TA, Gabai B, Melamed E, et al. Skin biopsy for assessment of autonomic denervation in Parkinson's disease. ***J Neural Transm (Vienna)*** 2006; 113: 1169-1176.
39. Fischer M, Gemende I, Marsch WC, Fischer PA. Skin function and skin disorders in Parkinson's disease. ***J Neural Transm (Vienna)*** 2001; 108: 205-213.
40. Schestatsky P, Ehlers JA, Rieder CR, Gomes I. Evaluation of sympathetic skin response in Parkinson's disease. ***Parkinsonism Relat Disord*** 2006; 12: 486-491.
41. Niemann N, Billnitzer A, Jankovic J. Parkinson's disease and skin. ***Parkinsonism Relat Disord*** 2021; 82: 61-76.
42. Ravn AH, Thyssen JP, Egeberg A. Skin disorders in Parkinson's disease: potential biomarkers and risk factors. ***Clin Cosmet Investig Dermatol*** 2017; 10: 87-92.
43. Ziemssen T, Reichmann H. Non-motor dysfunction in Parkinson's disease. ***Parkinsonism Relat Disord*** 2007; 13: 323-332.
44. Turkka JT, Myllyla VV. Sweating dysfunction in Parkinson's disease. ***Eur Neurol*** 1987; 26: 1-7.
45. Ke JQ, Shao SM, Zheng YY, Fu FW, Zheng GQ, Liu CF. Sympathetic skin response and heart rate variability in predicting autonomic disorders in patients with Parkinson disease. ***Medicine (Baltimore)*** 2017; 96: e6523.
46. Onder H, Korkmaz B, Comoglu S. The rapid recovery of the sympathetic skin response in a patient with Parkinson's disease with STN-DBS. ***Neurol Sci*** 2023; 44: 1077-1079.
47. Skorvanek M, Bhatia KP. The Skin and Parkinson's Disease: Review of Clinical, Diagnostic, and Therapeutic Issues. ***Mov Disord Clin Pract*** 2017; 4: 21-31.
48. Tomic S, Kuric I, Kuric TG, Popovic Z, Kragujevic J, Zubonja TM, et al. Seborrheic Dermatitis Is Related to Motor Symptoms in Parkinson's Disease. ***J Clin Neurol*** 2022; 18: 628-634.
49. Thiboutot D, Anderson R, Cook-Bolden F, Draelos Z, Gallo RL, Granstein RD, et al. Standard management options for rosacea: The 2019 update by the National Rosacea Society Expert Committee. ***J Am Acad Dermatol*** 2020; 82: 1501-1010.
50. Saunte DML, Gaitanis G, Hay RJ. Malassezia-Associated Skin Diseases, the Use of Diagnostics and Treatment. ***Front Cell Infect Microbiol*** 2020; 10: 112.