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Investigating olfactory and gustatory dysfunction in patients with restless legs syndrome: A comparative analysis with healthy controls

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Ethics Committee Approval
The study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital, İstanbul Turkey (Approval No: HNEAH-KAEK-2016-70).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: This study aims to examine the correlation between dopamine deficiency and olfactory dysfunction in patients with restless legs syndrome (RLS) and to juxtapose these findings with gustatory function. This comprehension of the relationship may illuminate the pathophysiology of RLS, suggesting possible therapeutic targets.
Methods: We included a total of 100 male participants aged 40 and older, comprising 50 healthy volunteers and 50 patients with RLS. Participants were recruited from the Neurology Clinic at Sultan Abdulhamid Han Training and Research Hospital between September 2016 and April 2017. We objectively assessed olfactory function using the Sniffin' Sticks Test Battery, while gustatory function was evaluated using the Taste Strip test—participants identified the flavors presented to them.
Results: The mean age of the RLS patient group was 52.5 years, while it was 52.7 years for the healthy group. Olfactory test scores were significantly lower in the RLS group compared to the healthy group (P<0.05). Likewise, gustatory test scores were also significantly lower in RLS patients (P=0.032). A strong positive correlation was observed between the olfactory and gustatory test results (r=+0.72), indicating a significant decline in both sensory functions in RLS patients.
Conclusion: This study reveals a significant association between dopamine deficiency, olfactory dysfunction, and impaired taste perception in RLS patients. These findings suggest that RLS may involve underlying neurodegenerative processes affecting sensory perception. Further research is crucial to shed light on RLS mechanisms, which remain partially understood, and guide the development of targeted therapeutic strategies.

Keywords: restless leg syndrome, olfactory dysfunction, gustatory dysfunction, sensory testing

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Introduction

Restless leg syndrome (RLS) is a disorder characterized by an intense, often indescribable dysesthesia in the extremities, predominantly the legs, coupled with an overwhelming urge to move them. This restlessness is particularly noticeable at night, interfering with sleep initiation, and can continue for several hours, intermittently lasting as long as 3–5 h in severe cases. Although RLS symptoms may occasionally affect only one side, they are typically bilateral and symmetrical. As a result, RLS significantly impairs sleep quality and frequently leads to chronic sleep disturbances [1].

The diagnosis of RLS primarily depends on a detailed patient history and extensive physical and neurological examination. The condition often presents with subtle symptoms, making diagnosis difficult; it is estimated that only one in four cases is accurately diagnosed [2]. While some diagnostic methods concentrate on involuntary movements during rest, a conclusive diagnosis is founded on set clinical criteria.

Several hypotheses have been proposed to explain the pathophysiology of RLS, including psychological factors, vascular elements, and peripheral and central nervous system pathologies. Psychological factors are thought to be significant due to the high prevalence of depression and anxiety among RLS patients. The vascular hypothesis suggests that the relief of symptoms through movement – which increases venous flow – results from the accumulation of metabolites in the legs. Peripheral nervous system pathologies are noted in many patients, even when neurological examinations reveal no structural lesions; RLS is also associated with polyneuropathy [3]. Akpınar et al. [4] first suggested central nervous system involvement, observing that dopaminergic hypofunction could help alleviate RLS symptoms with L-dopa [3]. The idea that motor restlessness in RLS stems from a lesion in the diencephalospinal dopaminergic system is supported by the successful outcomes of dopaminergic treatments [5].

Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disorder caused by the degeneration of dopamine-producing cells in the brain, leading to motor symptoms like tremors, slowed movements, muscle rigidity, and balance issues. These symptoms typically emerge between ages 40 and 75. The disease often goes undiagnosed for years, given its gradual onset and symptoms overlapping with other neurological conditions. The diagnosis of IPD relies on clinical criteria, as there are no definitive lab or imaging tests [6]. Motor symptoms manifest when the damage to dopamine cells exceeds 60%, progressing from the enteric nervous system to the substantia nigra and cerebral cortex. Non-motor symptoms such as loss of smell, sleep disturbances, and constipation may surface years before motor symptoms, signaling the early onset of the disease [7].

IPD, a neurodegenerative disorder typically presenting between the ages of 45 and 70, is more prevalent in men and characterized by bradykinesia, resting tremor, postural instability, and rigidity. Symptoms are often managed with L-dopa therapy. While IPD and RLS both respond to dopaminergic treatment, contrasting findings – such as dopamine deficiency in IPD and hypermetabolism in the substantia nigra in RLS – complicate a clear link [8]. Studies indicate men with RLS have a higher prevalence of IPD, yet recent research suggests RLS may serve as an early predictor rather than a direct risk factor for IPD [9]. Consequently, we hypothesize that taste and smell disturbances, an early sign of Parkinson's, might serve a similar role as an early indicator for RLS.

Materials and methods

This study encompassed male patients aged over 40 with RLS, who experienced RLS symptoms on 15 or more nights each month. Participants were selected from patients presented at the Neurology Clinic at the Sultan Abdulhamid Han Education and Research Hospital between September 2016 and February 2017, with institutional approval. The exclusion criteria included any condition or treatment known to impair taste or smell, depression as indicated by the Beck Depression Inventory, cognitive impairment assessed by the Mini-Mental State Examination, and a diagnosis of Parkinson's disease.

Testing Protocol

The Sniffin' Sticks Test, a validated olfactory assessment, was used to evaluate olfactory function. Resembling felt-tip pens, Sniffin' Sticks contain various odorants that are released upon cap removal, which allows for a controlled odor presentation. Patients were instructed to abstain from food and drink, except water, for at least 15 min before testing. The tests were conducted in a well-ventilated, low-odor room, with the examiner wearing odorless gloves (MediSense Burghart Sniffin' Sticks, 2016).

Test Procedure

For testing, patients wore a sleep mask, and single-nostril assessments were conducted by occluding one nostril with 3M Microfoam. The test involved holding the pen approximately 2 cm from the open nostril. The protocol consists of three stages:

1. **Threshold Test** – Establishes detection sensitivity using a dilution series,
2. **Discrimination Test** – Differentiates between similar odors,
3. **Identification Test** – Assesses the ability to recognize specific odorants.

Each segment – known as threshold, discrimination, and identification – was conducted with intervals of 3 to 5 min in between.

Threshold Test Methodology

The threshold test determines odor sensitivity via a "staircase" method. This method progressively presents increasing dilutions until the odor can no longer be distinguished. Pens numbered from 1 to 16 contain dilutions, with red-capped pens representing varying concentrations. During each trial, patients are presented with three pens in varying orders. These pens include one pen with the odorant and two with only the solvent. Patients start with the most diluted (or least odorous) sample and try to identify the different odors. For each correctly identified sample, an "X" is marked on the score form. Missed identifications, however, receive a "-". The test continues with sequentially stronger dilutions until the participant can identify the odor twice consecutively. This point establishes a detection threshold milestone, with subsequent milestones being recorded thereafter.

Threshold Test Calculation

In the threshold test, calculations are conducted to ascertain olfactory sensitivity, employing the arithmetic mean of the last four values (from positions four to seven) out of seven established threshold turning points identified by the patient.

Discrimination Test

The discrimination test evaluates the capacity to distinguish between odors. This is done by comparing groups of three presentations (triplets), where two pens have the same odor (non-target), and one pen (target) contains a differing odor. The patient's task is to identify the pen with the unique odor. The test comprises 16 triplets, each labeled with green numbers from 1 to 16. Target pens are identifiable through their green caps. Throughout the testing, patients receive verbal instructions – such as pen numbers – to smell each pen in the triplet and identify the distinct odor in every set.

Identification Test (Detection Test)

The identification test evaluates the patient's capacity to identify everyday odors using a multiple-choice format. In this test, the patient is given a card with four options and must pick the one that accurately corresponds to the smell they perceive. The test consists of 16 distinctive odors, labeled using blue numbers from 1 to 16. Patients are mandated to make a choice even if they struggle with the sense of smell or only perceive a faint odor (forced choice). For example, for item number 9, if the options are "onion, sauerkraut, garlic, carrot", the correct answer would be "garlic".

If the threshold score exceeds 1.0 (indicating the patient can differentiate between but/pea and solvent), the overall test result is obtained by adding up the scores from the threshold, discrimination, and identification tests (TDI). The TDI interpretation is as follows:

- A total TDI score greater than 30 indicates normosmia (normal sense of smell).
- A total TDI score greater than 16 indicates hyposmia (reduced sense of smell).
- A total TDI score of less than 16 indicates functional anosmia (loss of the sense of smell).

Taste Strip Taste Test

The "Taste Strip" test is a validated method for assessing taste perception. During the evaluation, strips infused with various flavors are placed on the patient's tongue while their mouth remains closed, thereby allowing the tongue to move freely. Before the test is conducted, it is crucial to ensure that patients have consumed only water, not smoked, and refrained from eating or chewing gum for at least 1 h. Each strip is intended for single use only.

Following the established protocol, 16 distinct taste strips are presented to patients in a random sequence. This includes both flavored and tasteless (blank - labeled as "U" and "V") strips. For example, an "Unpleasant" strip may be presented at the outset to acquaint the patient with the strip's taste. For a full-mouth evaluation, the taste strip is positioned at the center of the anterior third of the extended tongue. Patients are then instructed to close their mouths and gently move their tongues to prevent the strip from spinning or shifting. Between each taste test, a sip of water is used to cleanse the mouth.

After each strip is placed, patients are asked to identify the flavor they perceive, selecting from the options: "sweet", "sour", "salty", "bitter", or "unpleasant". Their responses are recorded on a summary sheet, with one point awarded for each correct identification. The maximum possible score on the test is 16, representing four correct answers for each taste type. The tasteless strips are not included in the evaluation. By summarizing the results, the overall taste performance and functionality for each specific taste quality can be assessed. Normative values for each taste type are provided in an accompanying table.

This study complied with the ethical standards delineated in the Declaration of Helsinki. The Haydarpaşa Numune Training and Research Hospital Ethics Committee granted ethical approval (Approval No: HNEAH-KAEK-2016-70). Furthermore, all participants provided written informed consent before their inclusion in the study, affirming their voluntary participation and understanding of the sensory testing procedures involved.

Statistical analysis

The statistical analysis was conducted using SPSS (Version 26.0, IBM Corp., Armonk, NY, USA). As the data were non-parametric, the Kruskal-Wallis H test was employed to compare differences in the TDI scores, and taste test scores among the healthy control group, RLS patients treated with dopamine agonists, and RLS patients treated with gabapentin. Whenever applicable, post-hoc analyses were utilized to pinpoint specific group differences. For the correlation analysis between odor and taste test scores, Spearman's rho correlation was used to determine the strength and direction of the relationship. A *P*-value of <0.05 was the threshold for statistical significance for all tests.

Results

Participants and Test Findings

In this study, we used the Sniffin' Sticks Test method to assess olfactory and gustatory function, exploring their potential relationship with RLS. Our participant pool consisted of 100 men, selected specifically to investigate if olfactory impairment could serve as an early indicator of Parkinson's disease. We required participants to be over the age of 40 and report more than 15 symptoms per month. Among the 100 participants, 50 individuals (50%) formed a healthy control group (Table 1).

The average age of the healthy group was 52.7 years, with all participants being male. This group included 12 smokers and 38 nonsmokers. On the other hand, the RLS cohort consisted of 50 male patients, who had an average age of 52.5 years and an average RLS severity score of 23.2. In this group, 18 patients were smokers, while 32 were nonsmokers (Table 1).

Table 1: Sociodemographic data.

	Healthy group	Patients with RLS
Age	52.7 (11.37)	52.5 (10.5)
Male/Female	50/0	50/0
Smoking/Non-smoking	12/38	18/32
HBS severity score	0	23.2 (11.2)
UPDRS	0	0
Total	50	50

Additionally, the 50 RLS patients were grouped into two categories based on their treatment: those undergoing dopamine agonist treatment and those treated with gabapentin. The majority, comprising 40 patients, or 80% of the RLS cohort, were on dopamine agonist therapy, while 10 patients, representing 20%, were treated with gabapentin (Table 1). The average age of all the participants was 52.7±8.1 years, with an average age of 52.2±7.9 years in the dopamine agonist group and 55±7.0 years in the gabapentin group (Table 1).

We conducted the Kruskal-Wallis H test to assess the significance of the decreases in TDI means among the groups. Results revealed a statistically significant reduction in each category (P=0.032). Specifically, TDI results showed that the RLS-PRD patient group had a TDI score of 32.5, while the healthy control group had a score of 37.5. Even though the RLS-PRD score remained within the lower limit of normosmia, the difference was statistically significant. Moreover, the threshold means disclosed an average of 8.3±1 in the healthy group, 8.0±1 in the dopamine agonist group, and a noticeably lower average of 6.4±0.7 in the gabapentin group. These findings underscore a significant decrease in threshold averages among selected participants (Table 2).

Table 2: Results of the difference test for decrease in threshold means.

Group	n	Mean rank	Chi-square	DF	*P*-value
Healthy group	50	73.50	74.668	2	<0.001
Dopamine agonist	40	31.45			
Gabapentin	10	11.70			

The Kruskal-Wallis H test was utilized to assess whether the decrease in mean threshold was significant, given the non-parametric characteristics of the data. We established that the decrease was indeed significant (P<0.001) (Table 2). Discrimination means were determined to be 14.8±0.8 in the healthy group, 12.1±2.3 in the dopamine agonist group, and 11.3±0.7 in the gabapentin group. These findings suggest that discrimination means a decline along with an increase in RLS severity. To confirm the statistical significance of the decrease in discrimination averages, the Kruskal-Wallis H test was re-administered. The results demonstrated significant changes in discrimination averages (P=0.032) (Table 3).

Table 3: Results of the difference test for reduction in identification means.

Group	n	Mean rank	Chi-square	DF	*P*-value
Healthy group	50	68.90	46.932	2	<0.001
Dopamine agonist	40	36.15			
Gabapentin	10	15.90			

The average TDI was 37.5 in the healthy group, 32.6 in the dopamine agonist group, and 28.8 in the gabapentin group. As such, the average TDI decreased proportionally to the increasing severity of RLS. Nonetheless, the average TDI remained at the normosmia level in the dopamine agonist group, while it dropped to the hyposmia level in the gabapentin group (Table 4). The Kruskal-Wallis H test was employed to evaluate the significance of the decline in TDI averages; it showed a significant difference (P<0.001) (Table 4).

Table 4: Results of the difference test for reduction in TDI means.

Group	n	Mean rank	Chi-square	DF	*P*-value
Healthy group	50	72.50	72.250	2	<0.001
Dopamine agonist	40	33.20			
Gabapentin	10	9.70			

Additionally, taste test averages were observed to be 15.4±0.6 in the healthy group, 12.5±2.4 in the dopamine agonist group, and 11.1±1.8 in the gabapentin group. Like the other sensory tests, taste averages decreased with increases in RLS severity. The Kruskal-Wallis H test was employed to determine if this decrease in taste averages was statistically significant. The results indicated a significant decrease (P<0.001) (Table 5).

Lastly, we analyzed whether a correlation existed between the averages of the odor and taste tests. Analysis by Spearman's rho correlation, suitable for non-parametric data, revealed a correlation coefficient of +0.72. This indicates a strong positive correlation between the odor and taste tests (Table 5).

Table 5: Results of the difference test for reduction in taste means.

Group	n	Mean rank	Chi-square	DF	*P*-value
Healthy group	50	71.66	64.005	2	<0.001
Dopamine agonist	40	33.33			
Gabapentin	10	13.40			

Discussion

This study is among the first to directly investigate olfactory and gustatory testing in patients with RLS, shedding light on the interrelationship between these sensory modalities. We hypothesized that neurodegeneration in the olfactory nerve might manifest early in this population. Consequently, we expected olfactory and gustatory impairments to emerge, attributing them to neuronal degeneration associated with RLS. Significantly, our results showed a reduction in olfactory and gustatory test scores among RLS patients, deemed at risk for neurodegenerative conditions. Interestingly, we observed a positive correlation between the findings of both olfactory and gustatory tests, implying that sensory impairments may occur concurrently in this patient group. Hence, these insights critically suggest that olfactory dysfunction could serve as an early indication of neurodegenerative processes in individuals suffering from RLS.

The comparative analysis showed that the average age of RLS patients over 40 was 52.5 years, while the average age of the healthy control group was slightly higher at 52.7 years. The TDI results for the RLS cohort were significantly lower at 32.5 compared to the healthy group's 37.5, even though they still fell within the lower limit of normosmia. This discovery contradicts the literature, as only one previous study by Adler et al. [10] reported olfactory dysfunction in RLS patients. In Adler's research, the patient's average age was 67, with a severity scale score of 8.7, which is higher than the 23.2 in our study. Moreover, while Adler used UPSIT for his study, ours applied the Sniffin' Sticks method, contributing to statistically significant results in our group. These variations bolster the notion that diverse pathophysiological mechanisms might exist among different RLS patient groups.

Furthermore, among the RLS patients, those receiving dopamine agonists had a mean age of 52.2 years, while those in the gabapentin group had a slightly higher mean age of 55 years. This observation aligns with the findings of Beaven et. al. [11] who reported an increased prevalence and severity of olfactory dysfunction with age, and use of gabapentinoid medications. When comparing the identification test averages, a significant reduction was observed: the dopamine agonist group averaged 12.5, and the gabapentin group averaged 11.1. This correlates with the observed decreases in TDI scores, which were 32.6 in the dopamine agonist group and 28.8 in the gabapentin group. While the TDI scores remained within the normosmia range for the dopamine agonist group, the gabapentin group fell into the hyposmia range. These results align with the findings of Doty et al. [12], who emphasized the neurotransmitter-related pathophysiology of olfactory disorders, suggesting that the dopamine agonist group yielded higher TDI scores compared to the gabapentin group.

Additionally, our findings revealed a significant decrease in taste averages, with the dopamine agonist group averaging 13.1, and the gabapentin group averaging 12.1. There was a strong

positive correlation of +0.72 between the TDI and taste test results, suggesting that these sensory modalities might fluctuate together. Although a mechanism underlying taste disorders remains elusive due to the scarcity of related studies, it is known that sweet afferent nerves largely project to the nucleus of the solitary tract (NTS). Notably, the absence of significant pathology in the medullary region among our RLS patients, coupled with the preservation of the NTS, raises questions about the potential influence of medication on taste function [13]. Factors such as poor oral hygiene and changes in salivary consistency may also play a role.

The clinical significance of our findings is considerable. Patients presenting concurrent olfactory and gustatory dysfunctions should be closely monitored for potential neurodegenerative disorders [15]. Regular follow-up visits might be necessary to assess changes in sensory function over time, allowing for early intervention when needed. Our study suggests that the sensory deficits observed in the RLS-PRD group could indicate a shared pathophysiology with Parkinson disease (PD), strengthening our initial hypothesis about the neurodegenerative implications of olfactory dysfunction in this patient population. The occurrence of concurrent sensory deficits in this clinically high-risk group calls for increased vigilance and potential screening for neurodegenerative diseases [16].

Limitations

This study possesses several limitations that must be taken into account. Firstly, the sample included only male participants over 40 years of age, which could limit the generalizability of our findings to other demographic groups, such as women and younger individuals. These groups may experience different patterns of RLS and sensory dysfunctions. Male participants were purposely chosen to minimize potential hormonal influences on olfactory and gustatory functions, as sensory perceptions can markedly vary between genders and across different age groups. This controlled sample permits a more focused examination of the impact of dopamine deficiency on sensory function in RLS [17].

Moreover, the lack of random sampling could introduce selection bias, potentially affecting the accuracy of the observed associations between dopamine deficiency, olfactory dysfunction, and gustatory impairments. Unmeasured factors such as dietary habits, oral hygiene, and lifestyle choices may also confound the results, as these variables can independently influence both taste and smell perception apart from RLS. The cross-sectional design of the study further limits our ability to establish causality between dopamine deficiency and sensory dysfunctions in RLS.

The overlapping use of dopaminergic and gabapentin treatments among the participants further complicates interpretation, as these medications may independently influence sensory functions. Future research with a larger, more diverse cohort and employing a longitudinal approach, along with more optimum control of confounding factors, would help to resolve these limitations and offer a clearer understanding of the causal relationships.

Conclusion

This study signifies a notable association between RLS and sensory dysfunction, which suggests that simultaneous olfactory and gustatory deficits may indicate neurodegenerative processes in RLS. Future studies should include diverse populations and evaluate additional confounding variables, such as dietary habits, treatment types, and lifestyle factors. This knowledge could aid in creating targeted therapeutic approaches and help to establish sensory testing as a potential premature marker for neurodegenerative diseases in RLS patients.

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