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RESEARCH ARTICLE

Evaluation of olfactory functions in essential tremor

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ABSTRACT

Objective: Recently, non-motor symptoms are increasingly recognized in patients with essential tremors. This study evaluates essential tremor (ET) patients' olfactory dysfunction, a notable non-motor symptom.

Method: This study included 34 patients with ET and 25 healthy controls. Participants underwent nasal examinations and the Connecticut Chemosensory Clinical Research Center (CCCRC) odor test.

Results: The ET patients had significantly lower CCCRC odor total scores (p=0.044) and odor threshold scores than the control group (p=0.007). However, both groups had similar CCCRC odor discrimination scores (p>0.05). While not statistically significant, a positive correlation was observed between the tremor duration and odor scores (p>0.05).

Conclusion: Our study demonstrates the impairment of olfactory functions in ET patients, reinforcing the notion of a neurodegenerative process. Further large-scale studies examining additional non-motor symptoms could provide deeper insights into the disease's pathogenesis.

Keywords: Essential tremor, olfaction, odor tests, neurodegeneration

INTRODUCTION

Essential tremor (ET) is a chronic, progressive movement disorder characterized by postural and kinetic tremor. Its prevalence increases with age, most commonly affecting the upper extremities (90-95%), head (30%), lower extremities (10-15%), and voice (20%) (1). Age and family history are significant risk factors for ET (2). Although the precise etiopathology of ET remains unclear, it is potentially linked to the loss of Purkinje cells in the cerebellum, abnormalities in the cerebello-thalamo-cortical tract, axonal swelling, and neurodegenerative findings, including Lewy body damage in the brain stem (3,4).

Recent studies have shown that the disease course of ET is not limited to tremors; rather, it encompasses cognitive disorders, sleep disorders, and psychiatric findings such as depression, anxiety, phobia, personality, and behavioral changes. Additionally, non-motor findings such as auditory and olfactory

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disorders have been found to accompany tremors in ET patients (1,5,6). Among these non-motor findings, the loss of olfactory function is a well-defined symptom, particularly in the early stages of Parkinson's Disease (PD). Olfactory dysfunction is also observed in other neurodegenerative diseases, including Alzheimer's disease, multiple sclerosis, motor neuron disease, and spinocerebellar ataxia (7,8). ET is considered a neurodegenerative disease due to its clinical progression and the pathways responsible for its pathogenesis (9).

Our study aimed to evaluate olfactory function, which can be affected by the early stages of neurodegenerative diseases.

METHOD

Study Participants and Procedure

In this study, 34 patients with ET and 25 healthy controls were included on a voluntary basis. The study was conducted in the Istanbul Training and Research Hospital Neurology outpatient clinic between January 2022 and December 2022. The inclusion criteria were an age range of 18-65 years and a confirmed diagnosis of ET according to the Consensus Statement of the Movement Disorder Society on Tremor (10). The exclusion criteria were: i) A history of medication use that could cause tremor; ii) Any pathology that might lead to tremor, as identified on cranial imaging; iii) Neurodegenerative diseases such as Parkinson's and related disorders; iv) Cognitive examination of the participants using Addenbrooke's Cognitive Examination Test, with exclusion of those scoring below 88; v) Patients with diseases related to the nasal cavity (acute/chronic sinusitis, history of nasal surgery); vi) Individuals using medical treatments that may adversely affect the sense of smell.

Written informed consent was obtained from all participants. The study was approved by the Istanbul Training and Research Hospital's local ethics committee (Institutional Review Board (IRB) approval date: 14.01.2022, number: 22) and conducted following the tenets of the Declaration of Helsinki for research involving human subjects.

The demographic data of the patients, family history of tremors, and medication history were collected. All patients underwent a detailed neurological examination. Additional information recorded, including the age of tremor onset in ET patients, initial tremor localization, tremor observation during the examination, progression of the disease process, and tremor severity according to the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) diagnostic criteria (+1, +2, +3). These criteria classified tremor severity into three stages: stage I as low amplitude, stage II as medium amplitude, and stage III as high amplitude (10).

Olfactory Assessment

The endonasal examination was conducted on all patients and healthy subjects participating in the study. The Connecticut Chemosensory Clinical Research Center (CCCRC) odor test, validated in Turkish by Veyseller et al. (11), was administered to eligible patients and healthy subjects. The CCCRC olfactory threshold test followed the protocol described in the literature. During the butanol threshold test, subjects were presented with two glass bottles containing water and a diluted butanol concentration (4% butanol in deionized water). Each subsequent dilution (nine glasses, decreasing from highest to lowest concentration) was a 1:3 dilution with deionized water. Four consecutive correct answers were considered the threshold. Scores ranged from 0 to 9, but all scores of 7 and higher were recorded as 7 for each test. For the odor detection test, eight stimulants (Vicks, baby powder, chocolate, cinnamon, coffee, naphthalene, peanut butter, and soap) were used in opaque jars, and odor discrimination was evaluated. The ability to sense Vicks indicates intact trigeminal nerve function. It was easily identified by all subjects and was not included in the final score. The odor discrimination and odor threshold scores were separately scored on a scale from 0 to 7 (0 being the worst, 7 the best), and the sum of these two values was recorded as the CCCRC total score (12).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0. Values were expressed as means, standard deviations, medians, extremes, frequencies, and ratios. The distribution of variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for analyzing quantitative independent data, while the chi-square test was employed for qualitative independent data, with the Fisher's test being applied when chi-square test conditions were not met. The Pearson correlation test was used for correlation analysis. The Kruskal-Wallis test was utilized for analyzing non-normally distributed groups. Statistical significance was assumed at a false detection rate of less than 5% ($p<0.05$).

Table 1: The demographic characteristics of the sample

	Patient group	Control group	p
Mean age (years±SD)	38.9±14.9	39.6±12.0	0.673[a]
Gender (n, %)			0.828[b]
Male	14 (41.2%)	11 (44.0%)	
Female	20 (58.8%)	14 (56.0%)	
Total (n %)	34 (100%)	25 (100%)	

SD: Standard deviation; a: Mann-Whitney U test; b: Chi-square test; p<0.05.

Table 2: Characteristics of tremors

	n	%
Family history of ET		
No	20	58.8
Yes	14	41.2
Tremor severity		
I	14	41.2
II	16	47.1
III	4	11.7
Tremor localization		
Bilateral	7	20.6
Right dominant	16	47.1
Left dominant	11	32.4

ET: Essential tremor.

RESULTS

The demographic characteristics of the ET patients and controls are summarized in Table 1. There was no statistically significant difference between the two groups regarding age and gender (p>0.05). The mean duration of the disease in the patient group was 6.2 years (range: 1-20 years). A family history of tremors was reported in 41.2% of the patients. Hand tremors were left-dominant in 32.4%, right-dominant in 47.1%, and bilateral in 20.6% of patients (Table 2). Head tremor was present in one patient.

The CCCRC total odor score was 10.4, and the odor threshold value was 6.2 in the patient group, compared to a total score of 11.9, and an odor threshold value was 5.3 in the control group (p<0.05) (Table 3).

There was no statistically significant difference between odor scores and gender (p>0.05).

No significant relationship was found between the presence of a family history of tremors and odor scores (p>0.05) (Table 4).

No significant correlation was observed between tremor severity and odor scores. However, an inverse and statistically significant relationship was found between the age of onset of the disease and the olfactory threshold, odor discrimination, and total scores (p<0.05). Though not statistically significant, a positive correlation was found between tremor duration and odor scores (r=0.38, p=0.05) (Table 5).

Table 3: Odor scores of the participants

	Control (n=25) Mean±SD	ET (n=34) Mean±SD	p[a]
Odor threshold	6.20±0.72	5.25±1.28	**0.007***
Odor discrimination	5.70±1.04	5.11±1.86	0.461
Odor total score	11.91±1.34	10.37±2.77	**0.044***

SD: Standard deviation; ET: Essential tremor; a: Mann-Whitney U test; *: p<0.05.

Table 4: Odor scores of the participants with and without family history of tremors

	With family history (n=14) Mean±SD	Without family history Mean±SD	p[a]
Odor threshold	4.72±1.19	5.62±1.25	0.870
Odor discrimination	4.90±1.86	5.25±1.91	0.912
Odor total score	9.63±2.54	10.87±2.89	0.540

SD: Standard deviation; a: Mann-Whitney U test; p<0.05.

Table 5: Correlation of tremor duration, age at illness onset, and odor scores in the patient group

	Mean tremor duration (6.2 years; range: 1-20 years)	Age at illness onset (mean±SD) (34.25±16.48)	Tremor severity (1-3)
Mean odor threshold (±SD) (5.25±1.28)			
r	0.28	0.38	0.36
p	0.14	0.05	0.17
Mean odor discrimination (±SD) (5.11±1.86)			
r	0.36	0.47	0.21
p	0.06	**0.01***	0.29
Total odor score (±SD) (10.37±2.77)			
r	0.38	0.5	0.31
p	0.05	**0.01***	0.55

SD: Standard deviation; r: Pearson correlation coefficient; *: p<0.05.

DISCUSSION

While ET was long considered benign, recent studies have identified it as a neurodegenerative disease with a progressive course, potentially accompanied by non-motor findings beyond tremor (5,13). Numerous studies have explored the presence of cognitive disorders, sleep disorders, depression, anxiety, phobia, personality and behavioral changes, and non-motor findings like auditory and olfactory dysfunction in ET, similar to other neurodegenerative diseases (5,14,15). In our study, we presented findings that non-motor symptoms may accompany ET.

Literature shows varying results regarding olfactory dysfunction and ET (16,17). In our study, we evaluated the olfactory functions of ET patients using the CCCRC odor test and found that ET patients had lower odor scores than the control group.

Louis et al. (16) found lower odor scores in ET patients than the control group in their study, which had a similar number of participants to ours. They further supported this result with a subsequent study that included a higher number of participants. Another finding in line with our study is that the severity of olfactory dysfunction appeared independent of tremor severity and duration (17).

However, our study observed a positive correlation between tremor duration and odor scores, although it did not reach statistical significance. Evaluating these results with a larger patient group could yield more precise conclusions.

In our study, 41.2% of patients had a history of tremors in their families, but their odor scores were similar to those without a family history of tremors. Doty et al. (18) identified a severe loss of olfactory function that increases with age, particularly in the sixth and seventh decades. This finding could indicate a potential negative impact of older age on odor results in other studies.

The inverse significant relationship between the age of disease onset and odor scores in our study supports this idea, suggesting that the relatively younger age of our patient group did not prevent negative impacts. This finding may suggest that the loss of olfactory function in ET patients is an age-independent result.

In a study examining gender-related differences in non-motor findings, the authors noted that the loss of olfactory function was more pronounced in females. However, this study focused only on PD patients (19). While no study in the literature compares this aspect of ET, our study found no statistically significant difference between genders.

Many studies have studied the relationship between ET and PD (20). The presence of similar clinical findings complicates the diagnosis for some patients. Studies have indicated that ET may be a risk factor for PD, leading researchers to continue efforts in differentiating these diseases. In addition to motor symptoms, such as characteristics, onset, and localization of tremors, many studies have recently been conducted on non-motor symptoms (21). These studies indicate that non-motor findings are more frequently observed in PD than in ET (22-25). Elhassanien et al. (26) suggested that olfactory function, one of these non-motor symptoms, can differentiate tremor-dominant PD from ET. However, Giorelli et al. (27) reported a non-significant difference in the number of non-motor symptoms between patients with PD and ET.

Both diseases involve a neurodegenerative process in their pathophysiology, but it is known that different pathogenetic pathways are affected in each disease group. As a result, different outcomes are observed in both clinical settings and studies (18-20).

Hawkes et al. (28) attributed olfactory dysfunction in PD primarily to Lewy body damage in the olfactory bulb, while Doty et al. (29) proposed it may be linked to decreased number of neurons in structures, such as the locus coeruleus, the raphe nuclei, and the nucleus basalis of Meynert. However, the olfactory dysfunction observed in ET is thought to originate from the cerebellar system, which represents a very different pathway (17,30).

The cerebellar system also plays a crucial role in the pathogenesis of ET, and its relationship with olfactory function has been demonstrated in multiple studies. For instance, Louis et al. (30) found that olfactory loss was also detected in patients exposed to a substance known to cause ET, termed 'blending'. They attributed this to the toxic effect of the blend on the cerebellum. Additionally, odor evaluations in different patient groups affected by cerebellar disorders also revealed the presence of odor loss. A functional Magnetic Resonance Imaging (fMRI) study further showed that the cerebellum plays a role in the sense of smell. These results support the hypothesis that the cerebellum is responsible for olfactory loss in ET (31-35).

The study by Altunisik et al. (36) evaluating the olfactory bulb volume and olfactory tract length in ET contributed data supporting both neurodegeneration and the involvement of the olfactory pathway.

Our study demonstrated a negative effect on the odor threshold of ET patients. This finding is considered one of the indicators supporting ET's neurodegenerative process. Further evaluation

of other non-motor findings and additional examinations of the cerebellar system will provide more evidence for this perspective.

While studies reporting normal olfactory functions in ET patients cannot be overlooked, the variation in ET pathogenesis, presentation, and progression suggests that the differing results may be related to the disease's heterogeneity (37). Undoubtedly, more descriptive studies involving larger patient groups are needed.

The limitations of our study include the limited number of patients, the small size of the control group, and the inability to evaluate olfactory function using detailed electrophysiological methods.

CONCLUSION

In conclusion, the significance of olfactory function, alongside other non-motor findings in ET patients, should be considered integral to understanding the neurodegenerative processes of the disease. Therefore, olfactory function assessment should be included in clinical evaluations from an early stage.

Contribution Categories		Author Initials
Category 1	Concept/Design	B.B.
	Data acquisition	Y.A.
	Data analysis/Interpretation	T.G.
Category 2	Drafting manuscript	B.B., R.G.G.C.
	Critical revision of manuscript	A.S., O.Y.
Category 3	Final approval and accountability	B.B, Y.A., R.G.G.C., T.G., O.Y., A.S.

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