Epilepsi 2020;26(1):25-29 DOI: 10.14744/epilepsi.2019.86648

ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Impaired Olfactory Function in Patients with Mesial Temporal Lobe Epilepsy Associated with Hippocampal Sclerosis


Dr. Mine SEZGİN

Hipokampal Skleroz ile İlişkili Mezial Temporal Lob Epilepsili Hastalarda Koku Duyusunun Değerlendirilmesi

Mine SEZGİN,[1] Bedia SAMANCI,[1] Cömert ŞEN,[2] Yavuz SAMANCI,[3] Nerses BEBEK,[1] Kadir Serkan ORHAN,[2] Betül BAYKAN[1]

[1]Department of Neurology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey
[2]Department of Otorhinolaryngology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey
[3]Department of Neurosurgery, Başkent University İstanbul Health Research and Application Center, İstanbul, Turkey

Summary

Objectives: It has been proposed that olfactory function disorders, such as parosmia or hyposmia, were associated with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). In this study, we aimed to compare the olfactory function and its subtypes between MTLE-HS and healthy controls.

Methods: We recruited 22 non-operated consecutive patients diagnosed with MTLE-HS and 22 aged and gender-matched healthy controls (HC). After a detailed clinical evaluation, we used a standardized tool, Sniffin' Sticks test, to evaluate the olfactory function.

Results: The mean age was 37.5 (±12.7) years in the MTLE-HS group and 36.9 (±10.3) years in the HC group. There were 14 females and eight males in both groups. Threshold, discrimination, identification and TDI scores were analyzed separately for each group. The threshold and discrimination values were similar in MTLE-HS and HC groups (p=0.063). Identification and TDI scores were significantly lower in the MTLE-HS group, respectively p<0.01 and p<0.001.

Conclusion: We have demonstrated the impaired olfactory function in MTLE-HS patients in the Turkish population. For the MTLE-HS patients, both peripheral changes, as well as structural or functional alterations in mesial temporal lobes and prefrontal lobes, have been proposed, and our results are in favor of central involvement.

Keywords: Mesial temporal lobe epilepsy; olfaction; Sniffin' Sticks test.

Özet

Amaç: Hiposmi, parosmi gibi koku duyusundaki çeşitli bozuklukların hipokampal skleroza bağlı mezial temporal lob epilepsisi (HS-MTS) ile ilişkili olduğu düşünülmektedir. Bu çalışmada, HS-MTS tanısı ile takip edilen hastaların koku fonksiyonlarının sağlıklı bireylerle karşılaştırılması ve koku duyusundaki değişimlerin ayrıntılı olarak tanımlanması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya HS-MTS tanılı, epilepsi cerrahisi öykü olmayan 22 hasta ile yaş ve cinsiyet eşlenmiş 22 sağlıklı birey kontrol grubu olarak dahil edilmiştir. Ayrıntılı klinik değerlendirme sonrasında, her iki grupta koku duyusunu değerlendirmek ve karşılaştırmak için Sniffin' Sticks koku testi kullanılmıştır.

Bulgular: HS-MTS grubunu yaş ortalaması 37.5 (±12.7); kontrol grubunun yaş ortalaması 36.9 (±10.3) idi. Her iki grupta 14 kadın ve sekiz erkek birey vardı. Koku duyusu değerlendirilmesi kapsamında koku eşik, koku ayrım ve koku saptama alt grupları hesaplanarak karşılaştırıldı. Eşik değer ve ayrım skorları her iki grupta benzer iken (p=0.063), EAS (eşik-ayrım -saptama) toplam skoru ve koku saptama skorları HS-MTS grubunda anlamlı şekilde düşük bulundu (p<0.01 ve p<0.001).

Sonuç: HS-MTS'li bireylerde koku duyusu belirgin şekilde etkilenmiştir. Katılımcı sayısı sınırlı olmakla beraber HS lateralizasyonu koku duyusundaki bozulma ile ilişkili olabilir. Koku duyusundaki mevcut etkilenim mezial ve temporal loblardaki yapısal ve/veya fonksiyonel değişimlere ikincil olabilir.

Anahtar sözcükler: Mezial temporal lob epilepsisi; koku; Sniffin' Sticks testi.

Submitted *(Geliş)*: 12.04.2019
Accepted (Kabul) **:** 17.06.2019
***Correspondence (İletişim)*:** Mine SEZGİN, M.D.
***e-mail (e-posta)*:** szgnmn@gmail.com

Introduction

Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is one of the most common focal drug-resistant epilepsies.[1] The diagnosis is established with auras, such as rising epigastric sensation, déjà vu and fear, indicating temporal lobe origin in conjunction with typical seizure semiology besides spikes in temporal regions in the EEG. Careful evaluation of structural imaging studies with MRI shows the increased signal in T2/FLAIR weighted images and hippocampal volume loss in T1.[2,3] Patients with MTLE-HS often have complicated febrile seizures in childhood. Functional neuroimaging studies with PET also show hypometabolism in mesial parts of temporal lobes.[4]

MTLE-HS is a heterogeneous clinical entity and besides frequent seizures, there are also cognitive and behavioral problems, interfering with social life.[5–7] It has been noted that some patients with MTLE-HS had olfactory symptoms in seizures like feeling unpleasant smells.[8] Human olfactory function is based on a complex system, which includes many anatomic regions such as the olfactory bulb, piriform cortex, entorhinal cortex, orbitofrontal cortices and also mesial temporal regions.[9] Since similar anatomical structures and limbic circuits are affected with MTLE-HS, these patients may experience olfactory hallucinations or parosmia.[10,11] Additionally, interictal olfactory dysfunction has been reported in patients with MTLE-HS in a handful of studies.[12–14] We hypothesized that the odor identification and discrimination are more significantly impaired than the odor threshold in patients with MTLE-HS compared to healthy controls due to the involvement of central olfactory structures and designed a systematic study to uncover ignored olfactory problems of these patients.

Materials and Methods

Study population

We recruited 22 non-operated consecutive patients diagnosed with MTLE-HS in our epilepsy center in six successive months of 2016. MTLE-HS diagnosis was based on the ILAE criteria and has been reassured by experienced epileptologists. Twenty-two age and gender-matched volunteers were included as a healthy control (HC) group. All subjects have signed the informed consent form. Ethical approval for this study was obtained from the local ethics committee.

Patients with previous epilepsy surgery and those patients with intellectual disability were not included in this study. Additionally, subjects with a history of any kind of nasal pathology and allergic rhinitis were excluded by a careful examination by the experts.

Mean disease duration was 21.54 (±17.13) years in the MTLE-HS group. All patients were on antiepileptic medication; four patients were using only one antiepileptic drug (AED), seven patients had two AEDs, and 11 patients were on three or more AEDs. Eighteen of 22 patients in the MTLE-HS group have drug-resistant epilepsy according to the ILAE report by Kwan et al.[15]

Three patients have bilateral hippocampal sclerosis in the MRI. There were six patients with right-sided MTLE-HS and 13 patients with left-sided MTLE-HS. All subjects were right-handed. We also asked for smoking status; there were seven smokers in the MTLE-HS group and six in the HC group (Table 1).

Evaluation of olfactory function

We used a standardized tool, Sniffin' Sticks test, to evaluate the olfactory function. Sniffin' Sticks test is an internationally recognized, widely used neurobehavioral tool for assessment of olfaction, allowing detailed, semi-objective evaluation of a patient's olfactory performance[16,17] which also has been validated in Turkish population.[18] The investigators were appropriately trained and used the Sniffin' Sticks test according to detailed instructions explained in a

Table 1. Demographic and clinical features

	MTLE-HS (n=22)	HC (n=22)
Age (y)	37.5 (±12.7)	36.9 (±10.3)
Gender (F/M)	14/8	14/8
Smoker (n)	7	6
MTLE lateralization		
Right	6	
Left	13	
Bilateral	3	
Disease duration (years)	21.54 (±17.13)	
Seizure frequency (n/year)	11.8	
Antiepileptic drugs		
≤2	11	
≥3	11	

MTLE-HS: Mesial temporal lobe epilepsy with hippocampal sclerosis; HC: Healthy control; F: Female; M: Male; n: Number.

previous study.[19] Participants were told not to smoke and not to drink coffee or tea 30 minutes before the test. None of the patients had a seizure within a day before the test. The study was performed in a quiet, odorless place and examiners washed his/her hands without using soap. In brief, the Sniffin' Sticks test (Burghardt®, Wedel, Germany) includes three subtests, ending up with four scores: threshold (T), discrimination (D), identification (I) and lastly TDI the global olfactory score, that is simply the sum of the previous three scores.

TDI scores lower than 30 points were defined as hyposmia.[16,19]

Statistical analysis

SPSS (Statistical Package for Social Sciences, SPSS Inc. Chicago, IL) version 21 was used for all statistical analysis. After normality analysis conducted using the Kolmogorov-Smirnov test, independent samples t-test and Mann-Whitney U test were used accordingly for parametric variables. We also used the chi- square test for non-parametric variables. The significance level was set as $p<0.05$.

Results

Demographic and clinical features of MTLE-HS and HC groups were shown in Table 1. Twenty-two patients with MTLE-HS and 22 HC were enrolled in this study. The mean age was 37.5 (±12.7) years in the MTLE-HS group and 36.9 (±10.3) years in the HC group. There were 14 females and eight males in both groups. Mean age and gender distributions and the number of smokers were similar in both groups.

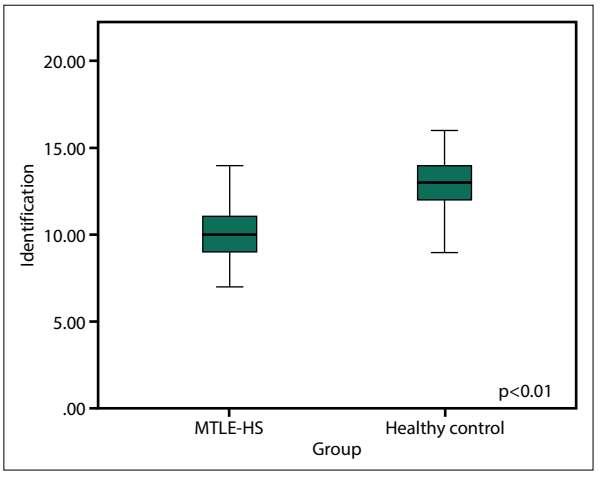

Fig. 1. Identification scores of MTLE-HS and healthy control groups. MTLE-HS: Mesial temporal lobe epilepsy with hippocampal sclerosis.

Threshold, discrimination, identification and TDI scores were analyzed separately for each group. The threshold and discrimination values were similar in MTLE-HS and HC groups ($p=0.063$). Identification and TDI scores were significantly lower in the MTLE-HS group, respectively $p<0.01$ and $p<0.001$ (Figs. 1 and 2).

There were 15 patients diagnosed with hyposmia in the MTLE-HS group and six subjects in the HC group. The differ-

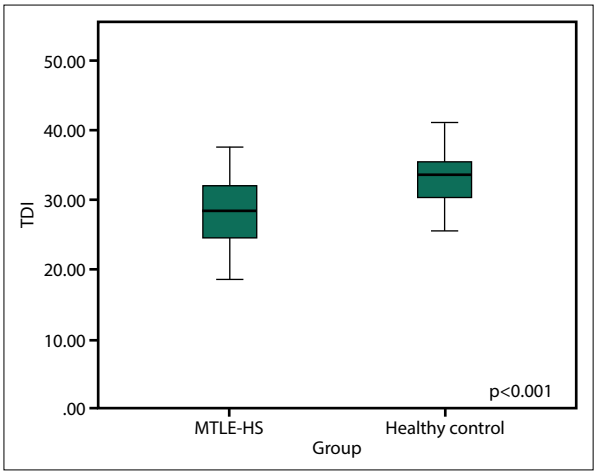

Fig. 2. TDI scores of MTLE-HS and healthy control groups. MTLE-HS: Mesial temporal lobe epilepsy with hippocampal sclerosis.

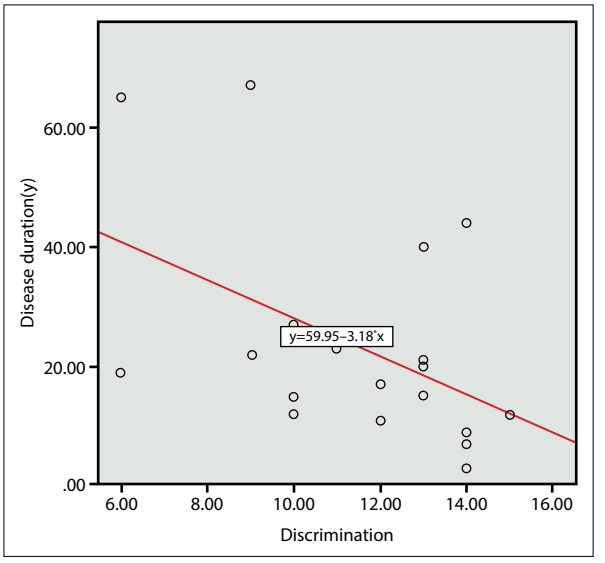

Fig. 3. Correlation analysis of disease duration and discrimination scores.

ence between groups was statistically significant (p=0.007) Because of the long disease duration of our study group (21.54 (±17.13) years), we assessed the correlation of olfactory test scores with disease duration in the MTLE-HS group. Although there were no correlations between disease duration and threshold, identification and TDI scores, odor discrimination and disease duration have a statistically significant linear relationship (p<0.05) (Fig. 3).

After the exclusion of three patients with bilateral MTLE-HS, we compared six right-sided and 13 left-sided MTLE-HS patients regarding the test subscores and found that the identification scores were statistically significantly different, showing more impairment in the right-sided MTLE-HS patients (p<0.05).

Discussion

In this study, we have systematically evaluated olfactory function in non-operated MTLE-HS patients compared to a matched HC group. We found lower identification and TDI scores in the MTLE-HS group while threshold and discrimination scores were similar in both groups, indicating the involvement of central olfactory structures supporting our hypothesis. This finding uncovers a neglected problem in this group of patients, emphasizing the need for awareness. Odor perception is one of the most important evolutionary protected means of interaction with the environment and plays major roles in human life, like social interactions and protection from danger. Thus, the comprehensive management plan of MTLE-HS patients should include olfactory testing to inform them for their highly possible but ignored defect.

Several conditions, such as upper respiratory tract infections, nose and paranasal sinus disorders, trauma and neurological diseases, may affect the olfactory function in humans.[20] Neurodegenerative diseases especially have a huge impact on olfaction. Patients with Parkinson's disease have olfactory dysfunction even at the earlier stages of the disease. Similarly, dementia, particularly Alzheimer's disease, may cause reduced olfactory function.[21] The underlying mechanism of olfactory dysfunction in neurodegenerative diseases has not been explained yet. Cortical changes, including prefrontal and temporal lobes, neurotransmitter alterations, reduced volumes of the olfactory bulb, have been proposed for the etiology of olfactory dysfunction in progressive neurological diseases.[22,23] For MTLE-HS patients, both peripheral changes (olfactory bulb volumes' changes), as well as structural or functional alterations in mesial temporal lobes and prefrontal lobes, have been proposed,[14,23] and our results are in favor of central involvement.

Compatible with our results, Desai et al.[24] found impaired smell identification and discrimination in 25 patients with TLE compared to 25 healthy subjects. In our small study sample, there was a statistically significant difference in the discrimination scores between right and left MTLE-HS. Hudry et al.[13] found that patients with left TLE had more difficulty with odor identification compared to right TLE. On the contrary, there was no difference in olfactory function between right and left TLE patients in another study.[24] These conflicting results may be due to small numbers of participants and the use of different kinds of neurobehavioral tools in different studies.

We detected a correlation between disease duration and odor discrimination, interestingly. Some studies have clearly indicated that there is progressive atrophy of the temporal lobe structures over time, but mainly in refractory TLE patients.[25] Another study reported continuing gray matter loss even in seizure-free patients as compared with normal controls.[26] Our findings supported the insidious progression of the MTLE-HS disease process, mainly in areas of the temporal lobe involved in olfaction.

Limitations

There are several limitations to this study. Firstly, because of the strict time limit of the Sniffin' Sticks test, we could collect a restricted number of non-operated subjects. The subgroup comparison of right versus left MTLE-HS should be interpreted with caution due to small numbers in these groups. Secondly, in this study, all MTLE-HS patients were on antiepileptic medications. Although it has been shown that antiepileptic drugs may help to restore olfactory dysfunction, such as parosmia in epilepsy,[27] we do not have satisfactory information about how antiepileptic drugs affect olfactory function overall.

In conclusion, we have demonstrated the impaired olfactory function in MTLE-HS patients in the Turkish population. We want to emphasize that the awareness of the identification problem of odors is important for the social life and protection of MTLE-HS patients. Future prospective studies are needed to uncover the underlying mechanisms and supply preventive measures in daily life.

Ethics Committee Approval
Ethics committee approved.

Peer-review
Externally peer-reviewed.

Conflict of interest
The authors declare that they have no conflict of interest.

Authorship Contributions
Concept: B.B., K.S.O.; Design: B.B., Y.S., K.S.O.; Data collection &/or processing: M.S., B.S., C.Ş.; Analysis and/or interpretation: M.S., B.S.; Literature search: Y.S., C.Ş., M.S.; Writing: M.S., B.B.; Critical review: B.B., N.B.

References

1. Skidmore CT. Adult Focal Epilepsies. Continuum (Minneap Minn) 2016;22(1 Epilepsy):94–115. [CrossRef]
2. Duncan JS. Imaging and epilepsy. Brain 1997;120 (Pt 2):339–77. [CrossRef]
3. Vanli-Yavuz EN, Erdag E, Tuzun E, Ekizoglu E, Baysal-Kirac L, Ulusoy C, et al. Neuronal autoantibodies in mesial temporal lobe epilepsy with hippocampal sclerosis. J Neurol Neurosurg Psychiatry 2016;87(7):684–92. [CrossRef]
4. la Fougère C, Rominger A, Förster S, Geisler J, Bartenstein P. PET and SPECT in epilepsy: a critical review. Epilepsy Behav 2009;15(1):50–5. [CrossRef]
5. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003;54(4):425–32. [CrossRef]
6. Gilliam F, Hecimovic H, Sheline Y. Psychiatric comorbidity, health, and function in epilepsy. Epilepsy Behav 2003;4 Suppl 4:S26–30. [CrossRef]
7. Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res 2000;39(2):121–5. [CrossRef]
8. Chen C, Shih YH, Yen DJ, Lirng JF, Guo YC, Yu HY, et al. Olfactory auras in patients with temporal lobe epilepsy. Epilepsia 2003;44(2):257–60. [CrossRef]
9. Eslinger PJ, Damasio AR, Van Hoesen GW. Olfactory dysfunction in man: anatomical and behavioral aspects. Brain Cogn 1982;1(3):259–85. [CrossRef]
10. Ciumas C, Lindström P, Aoun B, Savic I. Imaging of odor perception delineates functional disintegration of the limbic circuits in mesial temporal lobe epilepsy. Neuroimage 2008;39(2):578–92. [CrossRef]
11. Lehrner J, Baumgartner C, Serles W, Olbrich A, Pataraia E, Bacher J, et al. Olfactory prodromal symptoms and unilateral olfactory dysfunction are associated in patients with right mesial temporal lobe epilepsy. Epilepsia 1997;38(9):1042–4. [CrossRef]
12. Jones-Gotman M, Zatorre RJ, Cendes F, Olivier A, Andermann F, McMackin D, et al. Contribution of medial versus lateral temporal-lobe structures to human odour identification. Brain 1997;120(Pt 10):1845–56. [CrossRef]
13. Hudry J, Ryvlin P, Saive AL, Ravel N, Plailly J, Royet JP. Lateralization of olfactory processing: differential impact of right and left temporal lobe epilepsies. Epilepsy Behav 2014;37:184–90.
14. Haehner A, Henkel S, Hopp P, Hallmeyer-Elgner S, Reuner U, Reichmann H, et al. Olfactory function in patients with and without temporal lobe resection. Epilepsy Behav 2012;25(4):477–80. [CrossRef]
15. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069–77. [CrossRef]
16. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol 2007;264(3):237–43. [CrossRef]
17. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 1997;22(1):39–52. [CrossRef]
18. Tekeli H, Altundağ A, Salihoğlu M, Cayönü M, Kendirli MT. The applicability of the "Sniffin' Sticks" olfactory test in a Turkish population. Med Sci Monit 2013;19:1221–6. [CrossRef]
19. Rumeau C, Nguyen DT, Jankowski R. How to assess olfactory performance with the Sniffin' Sticks test(®). Eur Ann Otorhinolaryngol Head Neck Dis 2016;133(3):203–6. [CrossRef]
20. Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch Otolaryngol Head Neck Surg 2002;128(6):635–41. [CrossRef]
21. Mesholam RI, Moberg PJ, Mahr RN, Doty RL. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch Neurol 1998;55(1):84–90. [CrossRef]
22. Doty RL. Olfaction in Parkinson's disease and related disorders. Neurobiol Dis 2012;46(3):527–52. [CrossRef]
23. Hummel T, Henkel S, Negoias S, Galván JR, Bogdanov V, Hopp P, et al. Olfactory bulb volume in patients with temporal lobe epilepsy. J Neurol 2013;260(4):1004–8. [CrossRef]
24. Desai M, Agadi JB, Karthik N, Praveenkumar S, Netto AB. Olfactory abnormalities in temporal lobe epilepsy. J Clin Neurosci 2015;22(10):1614–8. [CrossRef]
25. Bernhardt BC, Kim H, Bernasconi N. Patterns of subregional mesiotemporal disease progression in temporal lobe epilepsy. Neurology 2013;81(21):1840–7. [CrossRef]
26. Alvim MK, Coan AC, Campos BM, Yasuda CL, Oliveira MC, Morita ME, et al. Progression of gray matter atrophy in seizure-free patients with temporal lobe epilepsy. Epilepsia 2016;57(4):621–9.
27. Caminiti F, De Salvo S, Nunnari D, Bramanti P, Ciurleo R, Granata F, et al. Effect of the antiepileptic therapy on olfactory disorders associated with mesial temporal sclerosis. Neurocase 2016;22(4):357–61. [CrossRef]