ARAŞTIRMAMAKALESİ/ORIGINALRESEARCH

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COVID-19 Enfeksiyonu İle İlişkili Önemli Bir Klinik Belirteç: Koku ve Tat Bozukluğu

An Important Clinical Marker Concerning COVID-19 Infection: Olfactory and Taste Dysfunction

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ÖZET

GİRİŞ ve AMAÇ: COVID-19 vakalarında koku ve/veya tat kaybı gibi minör ve nonspesifik bir semptomun olması, tanı için tek başına bir bulgu olabilir. Bu nedenle COVID-19 ile koku ve/veya tat kaybı arasındaki ilişkinin bilinmesi kritik bir öneme sahiptir. Özellikle major semptomları olmayan hastalarda akut koku ve/veya tat kaybının görülmesi, erken tanı ve izolasyonla birlikte viral yayılımın önlenmesi açısından yararlı olacaktır.

YÖNTEM ve GEREÇLER: Çalışmamızda Amerikan Otolaringoloji-Baş Boyun Cerrahisi Akademisi tarafından klinisyenler için geliştirilmiş ve validasyonu sağlanmış olan koku kaybı ölçümleme aracı esas alınarak kohort bir araştırma yapıldı.

BULGULAR: Bu çalışmada COVID-19 pozitif olan ve tat ve/veya koku kaybı görülen hastaların %40,4'ünde koku ve/veya tat kaybı şikayeti tanı konulmadan önce başladığı görüldü. Koku ve/veya tat kaybı prevalansının, cinsiyet ve yaş gruplarına göre anlamlı farklılık göstermediği saptandı.

TARTIŞMA ve SONUÇ: Bu çalışmada COVID-19 pozitif hastalarda koku ve tat kaybı semptomları literatürle uyumlu olarak anlamlı derecede yüksek oranda görülmüştür. Ayrıca Kulak Burun Boğaz kliniği açısından önümüzdeki dönemde de potansiyel COVID-19' a bağlı koku ve/veya tat kaybı vakaları görülmeye devam edecektir. Bu nedenle polikliniğe başvuran tüm hastalarda mutlaka koku ve/veya tat kaybının sorgulanması, yüksek risk taşıyan endoskopik muayene ve diğer işlemlerde dikkat edilmesi açısından çok önemlidir.

Anahtar Kelimeler: koronavirüs, covid-19, koku kaybı, olfaktör bozukluk, tat kaybı, koku alma

ABSTRACT

INTRODUCTION: The presence of a minor and nonspecific symptoms, such as loss of smell and/or taste in patients, may be a standalone symptom for the diagnosis of COVID-19 infection. Therefore, it is critical to know the relationship between COVID-19 and loss of smell and/or taste. Especially in patients without major symptoms, acute loss of smell and/or taste will be beneficial not only for early diagnosis and isolation but also for preventing viral spread.

METHODS: In our research, a cohort study was conducted based on the olfactory loss measurement tool developed and validated for clinicians by the American Academy of Otolaryngology–Head and Neck Surgery.

RESULTS: In 40.4% of cases, the complaint of loss of smell and/or taste was determined to present itself before the diagnosis of COVID-19. It was found that the prevalence of loss of smell and/or taste did not differ significantly depending on gender and age groups.

DISCUSSION AND CONCLUSION: In this study, symptoms of loss of smell and taste in COVID-19 positive patients were observed at a significantly higher rate in line with the literature. Additionally, in terms of Otorhinolaryngology clinic, it can be expected that potential cases of loss of smell and/or taste due to COVID-19 will continue to be seen in the future. For this reason, it is particularly important to question the loss of smell and/or taste in all patients who apply to the outpatient clinic, and to pay attention during endoscopic examination and other procedures that carry a high risk in possible cases.

Keywords: coronavirus, covid-19, loss of smell, olfactory dysfunction, loss of taste, olfactory

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INTRODUCTION

Odor loss may develop due to nasal inflammation, mucosal edema, and obstruction (1) in viral upper respiratory tract infections (URTIs), which are one of the major causes of odor loss. In most cases, the loss of smell improves with the regression of URTI symptoms, but in some cases, it can continue for months or even years (1). More than 200 types of viruses are known to cause olfactory dysfunctions. 10-15% of these were previously identified as coronaviruses. It is rarelv observed that coronaviruses. which are known to cause neurological, gastrointestinal, and respiratory diseases (2), cause loss of smell (3-5). It has been shown that the loss of smell is due to a neuroepithelial invasion from the olfactory bulb towards the central nervous system (1,5-10). It is known that millions of people around the world have been infected, hundreds of thousands of people have lost their lives due to the COVID-19 pandemic named as novel form coronavirus disease 2019 (COVID-19) by the World Health Organization(11). Along with the COVID-19 pandemic, there have been some publications (1,3-5,12) in the literature that loss of smell and taste may be among the symptoms in new COVID-19 patients. Especially patients who do not have major symptoms such as fever, cough and respiratory distress and therefore are not considered COVID-19 patients can cause the infection to spread quickly and easily. (5-6,12-13). The presence of a minor and nonspecific symptoms, such as loss of smell and/or taste in patients, may be a stand-alone symptom for the diagnosis of COVID-19 infection (1,3). Therefore, it is critical to know the relationship between COVID-19 and loss of smell and/or taste (5). Especially in

patients without major symptoms, acute loss of smell and/or taste will be beneficial not only for early diagnosis and isolation but also for preventing viral spread (1,3-5,12).

In our research, in order to reveal the symptomatic relationship between COVID-19 and loss of smell and/or taste in more detail and to determine its importance in the clinical course, a cohort study was conducted based on the olfactory loss measurement tool developed (14) and validated (15) for clinicians by the American Academy of Otolaryngology–Head and Neck Surgery. With this method, the demographic structure of the patients, risk factors, complaints, current infection status, the incidence of smell and/or taste loss and its relationship with other symptoms were investigated.

MATERIAL AND METHOD

This study was conducted with a total of 467 patients hospitalized with the diagnosis of COVID-19 at hospital between 01 September 2020 and 15 November 2020. The study was approved by local ethical commitee. Cases tested positive for COVID-19 with real-time polymerase chain reaction (RT-PCR) test by taking nasopharyngeal and oropharyngeal swab were included in the study. Cases, under 18 years of age, hospitalized in the intensive care unit, with a known history of sinonasal disease and/or surgery, smoking, and a history of head trauma were excluded from the study. Ethical approval was obtained from the local ethics committee. All participants were interviewed oneon-one, and their informed consent was obtained, and they were asked to answer the questions on the forms. Necessary measures were taken in order to protect the privacy of patient information in the forms. (Form 1).

COVID-19 RELATED ANOSMIA AND AGEUSIA DIAGNOSIS FORM NAME - SURNAME: 1) AGE: 2) GENDER: F FEMALE	8) Do you have a nasal sinus related disease? N No Y Yus 9) Have you undergone a nasal sinus related surgery? N No Y Yus 10) Have you experienced anosmia and/or ageusia before? N No Y Yus
Protect PY vs PX s PX s PX s PX s No State and the majory set of the formation of the state of the s	11) Are you experiencing sensory loss along with coronavirus disease? 13) Are you multiprespino an normal 21 have whith anomia and agausia. 21 have showing and agausia. 21 have anomia only. 21 have anomia 22 alog and presention from 1 at 0. 13 How anomia 2 alog anomia of a sectibe sour complaint of a genuin? Have anomia 2 alog alog alog alog alog alog alog alog

Form 1: Survey Form

Statistical Analysis

NCSS (Number Cruncher Statistical System) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. Pearson chi-square test, Fisher's exact test and Fisher-Freeman-Halton test were used to compare qualitative data. Statistical significance was assumed as p<0.05.

RESULTS

A total of 136 cases, 39.7% (n = 54) of which were female and 60.3% (n = 82) of which were male, were included in the study. (Table 1). The ages of the cases participating in the study ranged from 19 to 84, with an average of 38.69±12.94 years. It was recorded that 24.1% of the cases (n=26) were aged 19-29, 36.1% (n=39) were aged 30-39, 24.1% (n=26) were aged 40-49, 9.3% (n=10) were aged 50-59, and 6.5% (N=7) were aged 60 and over.50.7% (n=69) of the cases participating in the study, stated that they knew how the virus was transmitted, while 49.3% of which (n=67) did not know (Table 2). It was stated by the cases who knew how they got infected, 50% (n=62) of which were in close contact with someone diagnosed with Covid-19, 3,2% (n=4) of which were health workers, 12,9% (n=16) of which were living in a crowded environment, 17,7% (n=22) of which had been in crowded places and 1,6% (n=2) of which had travelled to areas that were known to be at high risk of contagion.It was observed that the most common complaint, other than loss of smell and/or taste, was fatigue in 66.2% (n=47) of the cases, and headache was the second most common complaint in 54.9% (n=39) of the cases. It was also observed that 31% (n=22) of the cases had high fever, 16.9% (n=12) had tremor, 28.2% (n=20) had dry cough, 66,2% (n=47) had weakness, fatigue, 21.1% (n=15)

COVID-19 and	Olfactory and	Taste Dysfunction	1

nasal congestion, 11.3% (n=8) rhinorrhea and 16.9% (n=12) other complaints (Table 2).It was determined that 29% (n=36) of the cases participating in the study had loss of smell and taste, 6.5% (n=8) had only loss of smell, 9.7% (n=12) had only loss of taste and in 54.8% (n=68) smell and taste functions were found to be normal (Table 3).40.4% (n=19) of the cases indicated the onset time of smell and/or taste loss before diagnosis, 36.2% (n=17) of them at diagnosis (Table 3). 51.1% (n=24) of the cases stated that the loss of smell and/or taste started to improve in 1-7 days after diagnosis, 8.5% (n=4) stated that the situation continued (Table 3).

According to the VAS score of the cases participating in the study, mean levels of olfactory loss were found to be 6.24 ± 3.27 with a median value of 7. Mild loss of smell was detected at 28.3% (N=13); moderate loss of smell was detected at 19.6% (n=9); severe loss of smell was detected at 23.8% (n=11) and complete loss of smell was detected at 28.3% (N=13) on the cases participated in the study (Table 4). Again, according to the VAS score, mean levels of taste loss were found to be 5.89±3,097 with a median value of 5. Mild loss of taste was detected at 22,4% (n=11); moderate loss of taste was detected at %34,7 (n=17); severe loss of taste was detected at 18,4% (n=9) and complete loss of taste was detected at 24,5% (n=12) on the cases participated in the study (Table 4).No statistically significant difference was found between the incidence of loss of smell and/or taste in cases according to age groups and gender (p>0,05) (Table 5). The rates of loss of smell and/or taste in the cases do not show a statistically significant difference, when compared to the complaints of fever, tremor, dry cough, weakness-fatigue, headache, nasal congestion, and rhinorrhea. (p>0,05) (Table5).

Age (n=108)	Min-Max (Median)	19-84 (38)
	Mean±Sd	38,69±12,94
	19-29 years	26 (24,1)
	30-39 years	39 (36,1)
	40-49 years	26 (24,1)
	50-59 years	10 (9,2)
	≥60 years	7 (6,5)
Sex	Woman	54 (39,7)
	Man	82 (60,3)

 Table 1: Distribution of Demographics

		n (%)
Know how they got infected		
	Yes	69 (50,7)
	No	67 (49,3)
Risk factors (n=124)	I	
	Being a health worker	4 (3,2)
	Being in close contact with someone diagnosed with Covid-19	62 (50)
	Living in a crowded environment	16 (12,9)
	Being in crowded places	22 (17,7)
	Travelling to areas known to be at high risk of contagion	2 (1,6)
	Other	12 (9,7)
	None of the above	17 (13,7)
Complaints (n = 71)		
	High Fever	22 (31,0)
	Tremor	12 (16,9)
	Dry Cough	20 (28,2)
	Weakness, Fatigue	47 (66,2)
	Headache	39 (54,9)
	Nasal Congestion	15 (21,1)
	Rhinorrhea	8 (11,3)
	Other	12 (16,9)

Table 2: Distribution of Disease-Related Situations

Table 3: Distribution of Situations Related to Loss of Smell and Taste

		n (%)
Loss of sensation with corona viru	us disease (n=124)	
	Smell and taste are normal	68 (54,8)
	There is a loss of both smell and taste	36 (29,0)
	There is only a loss of smell	8 (6,5)
	There is only a loss of taste	12 (9,7)
Time of onset of loss of smell and	i or taste (n = 47)	
	Before diagnosis	19 (40,4)
	At diagnosis	17 (36,2)
	After diagnosis	11 (23,4)
If the case has regained their abili	ity to taste and/or smell, when has it started (n=47)	
	1-7 days after diagnosis	24 (51,1)
	8-14 days after diagnosis	4 (8,5)
	Still continuing	19 (40,4)

Table 4: Distribution of Complaint Levels of Olfactory and Taste Loss

	Description for Olfactory Loss Complaint (n = 46)	Description for Taste Loss Complaint (n = 49)
Mean±Sd	6,24±3,27	5,89±3,09
Median (Min-Max)	7 (1-10)	5 (1-10)
	n (%)	n (%)
Mild loss	13 (28,3)	11 (22,4)
Moderate loss	9 (19,6)	17 (34,7)
Severe loss	11 (23,8)	9 (18,4)
Complete loss	13 (28,3)	12 (24,5)

		Loss of smell and/or taste		
		Absent	Present	
		n (%)	n (%)	р
Age	19-29 years	14 (53,8)	12 (46,2)	^a 0,070
-	30-39 years	16 (41,0)	23 (59,0)	
	40-49 years	16 (61,5)	10 (38,5)	
	50-59 years	8 (80,0)	2 (20,0)	
	≥60 years	6 (85,7)	1 (14,3)	
Sex	Woman	29 (53,7)	25 (46,3)	^b 0,325
	Man	51 (62,2)	31 (37,8)	
High Fever	Absent	23 (46,9)	26 (53,1)	^b 0,119
C	Present	6 (27,3)	16 (72,7)	
Tremor	Absent	24 (40,7)	35 (59,3)	°1,000
	Present	5 (41,7)	7 (58,3)	
Dry Cough	Absent	19 (37,3)	32 (62,7)	^b 0,326
	Present	10 (50,0)	10 (50,0)	
Weakness, Fatigue	Absent	13 (54,2)	11 (45,8)	^b 0,103
_	Present	16 (34,0)	31 (66,0)	
Headache	Absent	17 (53,1)	15 (46,9)	^b 0,057
	Present	12 (30,8)	27 (69,2)	
Nasal Congestion	Absent	24 (42,9)	32 (57,1)	^b 0,505
	Present	5 (33,3)	10 (66,7)	
Rhinorrhea	Absent	27 (42,9)	36 (57,1)	°0,458
	Present	2 (25,0)	6 (75,0)	

a)Fisher Freeman Halton Test b)Pearson Chi-Square Test c)Fisher's Exact Test **p<0,01

DISCUSSION

Treatment methods against coronavirus infection, for which no specific treatment has been found so far(16), are still being researched, meanwhile the symptoms of the disease are tried to be understood. In general, the relationship between smell and taste disorders and viral infections is a well-known phenomenon (17). Loss of smell can also rarely develop in infections due to coronaviruses (3-5). High fever, dry cough, shortness of breath, fatigue, myalgia and travel history to endemic regions were accepted as the primary symptoms in the first periods when the COVID-19 infection started to spread, and in time, complaints such as headache, sore throat, nasal congestion, loss of smell and/or taste have also begun to be reported (3,6,15,16,18), ultimately smell and/or taste disorder has also been suggested to be an important warning symptom (1,20-22). In a large literature study (4), it is reported that it is more common for COVID-19 to cause loss of smell and/or taste compared to other coronaviruses.

The pathophysiological mechanisms of olfactory dysfunction related to coronaviruses have not yet been fully elucidated (15). However, studies have shown that viruses spread from the olfactory bulb to the central nervous system via the transneuronal route (1,5,7,9,12,18), and that it is a neurotropic pathogen that can spread through the Virchow-Robin spaces surrounding arterioles and venules (7). In many studies (10,15,19,23,24), it has been shown that angiotensin-converting enzyme 2 (ACE2) receptors, which allow the virus to bind to and enter the epithelial cell, are widely found in the oral

mucosa, especially in the tongue mucosa, as in many different organs (19). In a study by Brann et al. (25), it was determined that the receptors, which allow COVID-19 to enter the nasal mucosa respiratory cells, were densely present. These findings indicate that nasal and oral mucosae are potential reservoir regions for virus infection. The exact diagnosis of COVID-19 is made by the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test (6,21,26).

In this study, AAO-HNS Anosmia Measurement Questionnaire was used to investigate odor and taste disorders associated with COVID-19 infection. (2). In addition, to determine hyposmia/dysgeusia, we asked the patients to rate the loss of smell and/or taste between 1-10 points in the related questions. Thus, we had the opportunity to examine the level of odor and/or taste loss in more detail (Table 4).

It is reported in the literature that loss of smell is more common in young and female patients who undergo the disease mildly and moderately (13,17,18,20). In our study, 60.3% of the cases with olfactory loss were male, 39.7% female, and the mean age was 38.69 (Table 1). There was no statistically significant difference in the frequency of loss of smell and/or taste between COVID-19 positive female and male patients (Table 5).

In the study of Giacomelli et al. (22), it was reported that at least one of the senses of smell or taste was lost in 33.9% of the cases, and both smell and taste were lost in 18.6% of the cases. In a study conducted by Yan et al. with 59 COVID-19 positive outpatients (5), it was found that 68% of the patients had loss of smell and 71% of them had loss of taste and found significant compared to COVID-19 negative control group. In this study, it was determined that 45.2% of the cases had smell and/or taste disorders(Table 3).

In many meta-analysis studies (4,27-28), it was found that the prevalence of loss of smell in hospitalized patients ranged from 5.1% to 66.7% and had inconsistent results. In fact, in another metaanalysis (23) conducted with five studies (a total of 1556 patients), it was reported that no loss of smell and/or taste was detected in patients, and deviations in patient selection were shown as the reason. In our study, the prevalence of olfactory disorder alone was 6.5%, the prevalence of taste disorder alone was 9.7%, and the prevalence of both olfactory and taste disorders was 29% in COVID-19 positive patients (Table 3).

In a study by Kaye et al. (15), it was reported that loss of smell occurred before the diagnosis of COVID-19 in 73% of the cases, and more importantly, it was the initial symptom in 26.6% of the cases, and it was suggested that the complaint of loss of smell was a preliminary symptom for PCR testing. In a study by Hopkins et al. (6), it was reported that loss of smell occurred before other symptoms in 13% of patients and in 38.4% it occurred simultaneously with other symptoms. Although, loss of smell can develop at any stage of the COVID-19 disease, but it is mostly observed during the initial period of infection. Studies have reported that most of the patients experienced loss of smell and/or taste in the prehospital period (17,20). Especially patients who do not have classic symptoms such as fever, cough and respiratory distress and therefore are not considered COVID-19 patients can cause the infection to spread quickly and easily (5-6,12-13).

In our study, the complaints of smell and/or taste disorders were present in 40.4% of the patients before the diagnosis, in 36.2% during the diagnosis, and in 23.4% after the diagnosis (Table 3). Additionally, it conspicuously appears that loss of smell and/or taste in COVID-19 patients develops without nasal congestion or other symptoms of rhinitis. This is probably due to direct viral damage to the olfactory and/or taste receptors (3). In our study, only 21.1% of the patients with olfactory loss had nasal congestion, 11.3% had rhinorrhea, and other patients did not have nasal congestion or rhinorrhea (Table 2).

In some publications (13,18,20-22) in the literature, conducting only telephone or online surveys with COVID-19 positive patients may create deficiencies in the answers given by the patients, such as not being able to remember some

symptoms and not being aware of the questionnaire. However in our study, we tried to increase the reliability of our study by excluding the related question from statistical evaluation in cases such as not being able to remember, not being sure, or not answering the question.

Brann, in his study (25), reported that olfactory damage is less common in younger patients compared to older age. In a study conducted by Ling et al. with 214 cases (10), it was reported that headache was found in 28 cases as a central nerve symptom and loss of smell and taste in 23 cases as a peripheral nervous system symptom. In our study, no statistically significant difference was found in the incidence of smell and/or taste disorders in COVID-19 positive patients in different age groups (Table 1). No statistically significant correlation was found between headache complaint and loss of smell and/or taste (Table 5).

Although the places of entry and proliferation of COVID-19 through droplets are the nose and mouth, the fact that sinonasal and oropharyngeal symptoms are less common than lower respiratory tract symptoms indicates that more research is needed. In addition, as the restrictive aspects of our study, it can be stated that there has been an inability to scan the entire population and determine the total number and rate of cases during the pandemic process, an inability to use objective tests because of the high risk of contagion (1),in addition to these the PCR tests are not 100% sensitive. However, the diagnosis of olfactory loss due to viral causes is primarily made by the patient's history (1).

In a study conducted by Yan et al. with 59 COVID-19 positive outpatients (5), it was observed that with the regression of general disease symptoms due to infection, the sensation of smell and taste improved in 18% within 1 week and 37.5% within 2 weeks. In the study conducted by Hopkins et al with 382 patients (13), it was reported that the loss of smell improved in approximately 80% of the cases within the first few weeks. In other publications (28), it is reported that the loss of smell in most patients shows rapid improvement within 7-10 days. In our study, the complaints of loss of taste and/or smell in 51.1% of the cases regained their ability to taste and/or smell within the first 7 days, in 8.5% of them within 8-14 days, and in 40.4% lasted more than 14 days. Therefore, in these cases, olfactory tests and treatment decisions for olfactory loss should be taken into account when improving within 7-10 days.

Conclusion

The results of all these studies and current data show that, although not all aspects have been clarified yet, COVID-19 infection significantly impairs smell and taste functions. As a result, in this study, symptoms of loss of smell and taste in COVID-19 positive patients were observed at a significantly higher rate in line with the literature. Although the loss of smell and/or taste is often seen to improve in the early period, larger studies are needed to determine how long the loss will last or whether it will be permanent. In conclusion, in this study, it is revealed that the loss of smell and/or taste, which develops suddenly and without any underlying cause, is a very important warning symptom for the diagnosis of COVID-19 infection and should be considered as a differential diagnosis criterion. Therefore, in the future, COVID-19 should be considered in the differential diagnosis of patients presenting with a new and sudden onset, isolated loss of smell and/or taste, and should be considered as a warning symptom for PCR testing. Additionally, in terms of Otorhinolaryngology clinic, it can be expected that potential cases of loss of smell and/or taste due to COVID-19 will continue to be seen in the future. For this reason, it is particularly important to question the loss of smell and/or taste in all patients who apply to the outpatient clinic, and to pay attention during endoscopic examination and other procedures that carry a high risk in possible cases. In asymptomatic patients, especially questioning the loss of smell will be useful in terms of early diagnosis and isolation, as well as prevention of virus spread.

Compliance with Ethical Standards

Funding: No funding was received for conducting this study.

Conflict of interest: The authorshavenorelevantfnancialornon-fnancial interest stodisclose.

Ethicalapproval:Thisstudywasperformed in linewiththe principles of theDeclaration of Helsinki. TheEthicsCommitteeApprovalwasobtainedfrom

Derince TeachingandResearchHospitalwiththe file number 2020-116.

Informedconsent: Allparticipantsgavetheinformedc onsenttotheuse of anonymizeddataprovided in theresponsestothequestionnaire.

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