

Covid 19 pandemic: Paranasal diagnostic imaging in patients with olfactory loss

Erkan Yıldız (✉ dr.erkanyildiz@hotmail.com)

Afyonkarahisar Şuhut State Hospital, Department of Otorhinolaryngology <https://orcid.org/0000-0002-0265-7327>

Aydın Balcı

Afyonkarahisar Healty Science University, Department of Chest Disease <https://orcid.org/0000-0002-6723-2418>

Okan Selendili

Manisa Alaşehir State Hospital, Department of Chest Disease <https://orcid.org/0000-0002-4902-974X>

Selçuk Kuzu

Afyonkarahisar Healty University, Department of Otorhinolaryngology <https://orcid.org/0000-0002-0511-9874>

Research Article

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Abstract

Objective: COVID-19; It is an infectious disease that starts with cold symptoms and causes Acute Respiratory Failure, causing deaths all over the world. Besides the common symptoms of the disease such as fever, dyspnea and cough, recently, a “sudden loss of smell” has been added as a diagnostic symptom.

Materials and Methods: Clinical and demographic features, Tomography results, and odor test scores of 40 patients diagnosed as sudden olfactory loss using Connecticut (CCCRC) Olfactory Test “will be evaluated together, and odor disorder and clinical and radiological findings will be compared.

Results: There was no significant difference in smell loss in terms of gender. No relationship was found between smoking and degree of smell disorder. ($p > 0.05$) When we evaluated the paranasal CTs taken from our patients with odor loss, 2 patients' CT showed pathological findings ($p < 0.05$). As the patients' illness worsened, an increase in the degree of odor loss was observed ($p < 0.05$). Between the CCCRC score and presence of PNS CT findings, a significant statistical relationship was found ($p = 0.0012$)

Conclusion : Olfactory loss was not related to age, gender, smoking. PNS CT findings were significantly correlated with the degree of olfactory loss. In patients with olfactory loss, evaluation with a PNS CT may be diagnostic in terms of COVID-19. However, in order for this examination to be diagnostic, a larger patient series is needed.

Introduction

New Coronavirus disease (COVID-19) is an infectious disease caused by the SARS- CoV-2 virus , which started in Wuhan, China and spread all over the world[1]. Coronavirus disease has been declared as a pandemic by the World Health Organization (WHO) on March 11, 2020[2]. It starts as a mild respiratory infection in most people. It is quite severe in patients with chronic disease such as hypertension, diabetes, chronic renal failure, asthma, Chronic obstructive pulmonary disease (COPD) and patients with advanced age. The most common symptoms of the disease are fever, cough, headache, myalgia, dyspnea and diarrhea[3]. Smell and taste disorder started to draw attention as the symptom that started as the earliest and ended as the latest[4]. The disease starts as a simple respiratory infection and causes pneumonia in a short time. The virus, which causes the radiologically ground glass appearance in the patient's lung, progresses to ARDS (Acute Respiratory Distress Syndrome) and causing deaths[5]. In diagnosis, a rapid antigen test or a SARS-CoV-2 identification with Polymerase Chain Reaction (PCR) is used. There is no specific treatment for COVID-19 disease. Although treatment guidelines vary from country to country, hydroxychloroquine therapy, azithromycin, favipiravir, lopinavir + ritonavir, remdesivir, ivermectin and tocilizumab drugs such as plasma treatment is used. Although effective medication and treatment-seeking studies continue, the gold standard treatment has not been established yet[6–8].

COVID-19 infects the respiratory epithelium. Hence it starts with symptoms in this area. In the Coronavirus epidemic, the most noticeable symptom recently has been the loss of smell and taste[9].

Recently, reports of hyposmia or anosmia have been declared from many countries. The olfactory loss rate in COVID-19 is between 34-68%. Otolaryngologists thought it might be a strong and early marker of COVID-19 infection, focusing on loss of smell and taste[10, 11].

Post-viral olfactory loss has been described in many viral infections. Post-viral olfactory dysfunction (PVOD) is the most common cause of acquired olfactory dysfunction[12, 13]. Post-viral olfactory dysfunction is mostly caused by Rhinoviruses, Influenza, Parainfluenza and older types of Coronaviruses[14]. COVID-19 may also appear as the first symptom. The cause of this loss can be considered as mucosal inflammation and edema in the nose and complete closure of the airway in the olfactory region. It is not yet known whether smell loss is long-term in COVID-19. However, in some patients, it has been reported to continue even after the disease has passed[4, 10]. Although there are many new studies on COVID-19 related to loss of smell, no study has yet been conducted on the radiological findings in the paranasal sinuses[4, 10, 11]. In our study, patients who had olfactory loss in COVID-19 were tested both for smell and the olfactory regions were examined by taking Paranasal Sinus Tomography (CT). The most frequently used scent tests are "The University of Pennsylvania Smell Identification Test (UPSIT)", "Connecticut (CCCRC) Olfactory Test", "Sniffin 'Sticks" Olfactory Test "[15–17]. In our study, we used the Connecticut (CCCRC) Olfactory Test, which is easy and fast to apply, and we tried to elucidate the pathophysiology of COVID-19 olfactory disorder by comparing the degrees of odor disorder and radiological findings.

Materials And Methods

In this study, 40 patients diagnosed with COVID-19 in our center between March 2020 and May 2020, and who have a smell disorder, were evaluated. Any of these patients who previously had either an acute smell disorder that prevented smell due to any otolaryngology disease (chronic rhinosinusitis, allergic rhinitis, nasal polyposis, a deviated septum etc.) or Alzheimer's disease, or non-chronic smell disorders such as Parkinson's disease, or drug- induced smell disorders, were not been selected as patients. Patients in the study with fever, malaise, myalgia, dyspnea and cough as known Covidien-19 symptoms, as well as acute olfactory dysfunction since a month, and was diagnosed via the Polymerase Chain Reaction (PCR) with Covidien-19 as processor was selected as a patient. The diagnosis of PCR was made with Applied Biosystems GeneAmp® PCR System 9700 device (Thermo Fisher Scientific, USA). Olfactory regions were interpreted radiologically by evaluating the Paranasal Sinus Tomographs (CT) of COVID-19 patients, who were referred to otolaryngology due to odor disorder. Those with complaints of olfactory disorders were diagnosed by making an odor test. A two-stage "Connecticut (CCCRC) Olfactory Test" was used for the odor test. The CCCRC test was performed in two stages as a butanol threshold test and an odor identification test as previously described. In the CCCRC test, scores below 5.75 were considered as olfactory disorders. It was accepted that the degree of odor loss in the disease increased as the CCCRC test score decreased. In addition, these patients were evaluated in terms of age, gender, smoking, additional disease, disease severity, treatments and mortality . The degree of the disease was divided into 1) mild (no pneumonia or mild pneumonia), 2) moderate (dyspnea, hypoxia or severe progress in lung findings within 24 hours), and 3) severe (respiratory failure, shock, multi organ failure).

Permission to study was given by the University of Health Sciences Afyonkarahisar Non-invasive Clinical Research Ethics Committee from (05.11.2020 / KAEK-2-2020-5) and the Republic of Turkey Ministry of Health, the Scientific Research Commission (29/04/2020) . The study was carried out in accordance with the Declaration of Helsinki.

Diagnosis and Treatment of COVID-19

COVID-19 diagnosis and treatment for the Republic of Turkey Ministry of Health Science Board has benefited from COVID-19 guidelines. Accordingly, patients with complaints such as fever, weakness, joint pain, headache, shortness of breath, cough, smell and taste disorder, and diarrhea were given a nasopharyngeal swab in the isolation rooms and diagnosed with a PCR device for the SARS-CoV-2 virus. Among these patients, an odor test was performed on patients with an odor disorder (hyposmia-anosmia) and a Paranasal Sinus CT was also taken. The “Connecticut (CCCRC) Olfactory Test” was used for the odor test. CT examinations with the device (MSCT, Philips Brilliance ICT 256; Philips Medical Systems, Netherlands) were performed on paranasal sinus with CT sections taken at 2 mm intervals (512x512matrix, voltage 100 kV, current 150 mAs). The images were made by bringing the head to hyperextension while the patient was in the prone position. Coronal CT sections were used for examination. Soft tissue thickening and fullness in the olfactory region of the paranasal Sinus CT coronal sections were accepted as positive tomography findings. Hydroxychloroquine tablets 2 * 200 mg (5 days) + Azithromycin tablet (500 mg tablet was given on the first day, and then for next 4 days, 250 mg / day was given as treatment, with Favipiravir 200 mg tablet (2 x 1600 mg loading, 2 x 600 mg) for patients with severe pneumonia. All drugs were used for 5 days.

“Connecticut (CCCRC) Olfactory Test”

1) Butanol Threshold Test

For each trial, two identical glass bottles were presented to the patient. Solutions with a concentration of water and diluted butanol in one bottle were marked. The patients were asked to smell by plugging the single nostril and approaching the bottle with the tip of the nose. The strongest bottle of butanol contained 4% butanol. (Bottle 1) A total of 7 bottles were prepared by diluting 1/3 with deionized water. Results were scored between 1-7 for the CCCRC test.

2) Identification Test

In this test, opaque bottles containing scents such as soap, peanut butter, naphthalene, Vicks, chocolate, coffee, cinnamon and baby powder, burnt paper, wood chips, peanut butter, mint, naphthalene, grape jam, ketchup, black pepper and rubber were smelled according to their sharpness. Participants were asked to score between 0-7. Finally, the CCCRC test score was calculated by taking the average of Butanol threshold test and identification test scores. Scoring was as follows: Normosmic: 6.00–7.00, Mild hyposmic: 5.00–5.75, Moderate hyposmic: 4.00–4.75, Severe Hyposmic: 2.00-3.75, and Anosmic: 0-1.75.

Statistical Analysis

All values were calculated as mean \pm standard deviation. The measurement-evaluation and statistical analysis methods of the research was as follows: the data obtained was evaluated with descriptive statistics (Arithmetic mean, median, standard deviation, percentage distributions). When comparing the mean between groups, the normal distribution suitability was first evaluated by the Kolmogorov Smirnov and Shapiro Wilk tests. When comparing the percentage distributions of categorical data between groups, a Chi Square test and one way anova were used. SPSS 22.0 (IBM SPSS Statistics , Chicago, USA) was used for data analysis. $p < 0.05$ was considered statistically significant.

Results

20 of the total 40 patients were male and 20 were female. The average age was 47.58 ± 20.57 years old, 46.00 ± 22.56 years old for males, and 49.18 ± 18.81 years old for females. There were 22 smokers(55%) and 18 non-smokers patient(45%). From clinical findings, there were 22 patients with fever (55%), 28 with headache (70%), 26 with cough (65%), 26 with dyspnea (65%), 19 with myalgia (47.5) and 3 patients with other symptoms (diarrhea, abdominal pain, etc.) (7.5). Patients were divided into 4 groups according to the odor test results and CCCRC test score. Mild hyposmia was detected in 13/40 (32.5), moderate hyposmia in 13/40 (32.5), severe hyposmia in 9/40 (22.5), and anosmia in 5 (12.5) patients. There were 2 patients with positive PNS CT findings (soft tissue or drainage disorder in the olfactory region) (2.5) (Figure 1a, 1b). There were 12 patients (30%), 20 patients (50%) and 8 patients (20%) graded according to the severity of the disease. There were 11 patients with hypertension, 9 with diabetes mellitus, 3 with COPD (Chronic obstructive pulmonary disease) , 1 with asthma, 1 with multiple sclerosis, 1 with Alzheimer's, 1 with Epilepsy, and 1 with Heart Failure. 11 patients did not have additional diseases. Hydroxychloroquine was given to all patients in the treatment. 36 patients (100%) were given Enfluvir, 6 patients were given Azithromycin and 3 patients were given Favipravir. Three patients needed intensive care and these 3 patients died.(Table 1,2,3)

Figure 1a, 1b: Paranasal Sinus CT Images of patients with olfactory loss:2 patients with sudden loss of smell have soft tissue thickening at the entrance of both olfactory regions in Paranasal Sinus CT (indicated by the red arrow)

Table 1: Demographic and clinical characteristics of patients with COVID-19 with olfactory loss

Table 2: Patients' degree of olfactory disorder and findings in the Paranasal Sinus CT

Table 3: The relationship between severity of the disease and degree of olfactory disorder and Paranasal Sinus CT Findings

According to the statistical results of our study:

- 1) In our study, a relationship of the disease to gender was not detected. ($P > 0.05$)
- 2) Advanced age and additional diseases have been influential in mortality. ($p < 0.05$, $p = 0.046$, respectively)

- 3) No relationship was found between smoking and degree of smell disorder. ($p > 0.05$)
- 4) When we evaluated the Paranasal CTs taken from our patients with odor loss, pathological findings were observed in the CT of 2 patients (anosmic) and were statistically significant ($p < 0.05$).
- 5) As the patients' illness got worse, the degree of odor loss increased ($p < 0.05$)
- 6) A statistically significant relationship was found between CCCRC score and presence of PNS CT findings ($p = 0.012$)

Discussion

Coronavirus (Covid-19) disease is a highly contagious infectious disease caused by the SARS-CoV-2 virus. Basically, it can be transmitted from animal to human and from person to person via droplets. The incubation period of the disease is about 1-14 days (average 5.2 days). Coronavirus is highly resistant to external environments due to it being an enveloped virus, and it has been revealed in various studies that it can live on inanimate surfaces for up to 14-21 days. The disease started in Wuhan, China at the end of December 2019, and spread to all continents in a short time and was declared as a pandemic by the World Health Organization (WHO) in March 2020. As of May 2020, nearly 4 million cases and nearly 300,000 deaths have been reported[18–20].

COVID-19 disease affects the respiratory epithelium. The disease starts like a cold and can turn into pneumonia in a short time. If the disease progresses further, it progresses to Acute Respiratory Distress Syndrome (ARDS) and leads to mortality. It is believed that viral load is important in worsening the illness. The viral load was reported to be highest in the lower respiratory tract – in the bronchoalveolar fluid (93%), secondarily in the upper respiratory tract, nasopharynx (60%), and thirdly in the pharynx (30%). The disease is diagnosed by bronchoalveolar lavage fluid, nasopharyngeal or swabs from the oropharynx, via an RT-PCR test. In addition, it can be diagnosed as a rapid antigen test with serological methods. The disease has been reported to be more severe in males, smokers, elderly and those with additional diseases[21]. In our study, the relationship of the disease to gender was not detected. Elderly and additional diseases were influential in mortality ($p < 0.05$, $p = 0.046$, respectively). No relation was found between smoking and the degree of smell disorder. ($p > 0.05$)

Imaging in COVID-19 pneumonia is much more important than many viral diseases. There are even authors who report that the disease is as important as the PCR test. The classic finding in thorax CTs that are routinely seen in patients is the “ground glass view”[22, 23]. COVID-19 recently reported cases with pulmonary imaging, Abdomen CT and Brain CT. Encephalitis has been reported in the brain as in some viral infections. A possible way for this to occur is via nasopharynx, sphenoid sinus, frontal sinus and cerebrospinal fluid[24].

Post-viral odor loss has been identified in many viral diseases, primarily Influenza and Rhinoviruses[12–14]. Patients with sudden olfactory loss were even reported in the MERS- CoV outbreak in 2012[25]. In the

COVID -19 pandemic, which started in China on December 2019, patients with sudden olfactory loss have been reported in countries such as China, Italy, Spain, Singapor and USA where pandemics are frequently seen. The rate of 5% was seen in a study in China and The American Academy of Otolaryngology-Head and Neck Surgery" in the study were reported as striking as the first symptom in 73% Health 26.6% patients.[25– 28]

It is obvious that the disease causes much more olfactory disorders than other viral infections. In this, the direct damage to the olfactory epithelium of the virus or the neural retrograde pathway can have an effect on the olfactory region containing the odor receptors in the region. From a study, the nucleic acid of the virus has been detected in both the brain tissue and the cerebrospinal fluid (CSF) [29, 30]. In the spread of the virus in the body, into many tissues and nervous system of the body, the angiotensin converting enzyme 2 (ACE 2) and transmembrane serine protease 2 (TMPRSS2) proteins plays a role. However, in a new study, it was shown that ACE 2 and TMPRSS2 proteins were not found in the olfactory region in humans. Therefore, there is no role of these proteins in olfactory damage. On the contrary, damage to basal cells was detected. Therefore, the possible mechanism in olfactory disorder appears to be the damage of these cells. Therefore, the biochemical reaction in the formation of odor cannot take place[31–34]. In our study, when we evaluated Paranasal CTs taken from patients with odor loss, pathological findings were observed in 2 patients' CT and were statistically significant ($p < 0.05$).

Since odor disorder is a subjective concept, objective tests were needed in its diagnosis. There are two types of odor tests, psychophysical and electrophysiological tests. In the diagnosis of smell disorder, smell tests are used in practice. These tests are carried out in two stages as odor threshold tests and odor odorant tests. In the threshold determination test, a scent bottle containing fragrances such as phenyl ethyl alcohol (PEA) or butyl alcohol (butanol) 4% and another bottle containing only water are presented to the patient. Odor detection tests are quantitative tests. Patients are asked to identify fragrances above the threshold. The most used of these are The University of Pennsylvania Smell Identification Test (UPSIT), Sniffin' Sticks, Connecticut odor detection test-CCCRC, OSIT-J (Odor Stick Identification Test for Japanese, Daiichi Yakuhin, Co., Tokyo, Japan), B-SIT (the Brief Smell Identification Test) and the Crosscultural smell identification test (CC-SIT). The most widely used of these tests is the UPSIT test[10, 15, 35]. These tests can also be used in the diagnosis of olfactory disorders in COVID-19 . In a study, the UPSIT test was used in patients with COVID-19 smell disorder, and according to this test, most patients were found to have a loss of smell ranging from mild microsmia to anosmia. The test scores were not related to age, degree of disease, nor additional diseases[10]. In another study, a smell and taste change survey was conducted on social media, and a significant result for COVID-19 was found in those with this symptom[35]. In our study, the CCCRC test, which is more suitable for Turkish society, was used. A correlation was found between both clinical and PNS CT finding on the positivity of the CCCRC score. As patients' illness worsened, an increase in olfactory loss was observed ($p < 0.05$). A statistically significant relationship was found between the CCCRC score and PNS CT findings ($p = 0.012$).

In literature, single Paranasal imaging in patients with COVID-19 with olfactor impairment has been reported in a single patient in the USA. A thickening and drainage disorder in the olfactory region was

reported in this patient in coronal sections. It is estimated that the olfactory bulb is retained through the cribriform plate depending on the involvement of the respiratory epithelium in patients with COVID-19[11]. In a study related to post-infectious olfactory loss, the infection-related olfactory bulb volume was shown to decrease³⁸. In our study, in the majority of patients with COVID-19 with olfactory disorders, obstructive thickening and loss of aeration were observed, especially in the Paranasal Sinus CT, which disrupted the olfactory region drainage. Thus, the cause of olfactory loss in these patients was confirmed by imaging. In addition, a significant relationship was found between the degree of odor disorder and the positivity of CT findings.

Since there were 40 patients in the study, the study needs to be done in larger series and in multiple centers.

Conclusion

COVID-19 is a disease that causes pneumonia illness and causes serious mortality, such as respiratory failure, from common cold symptoms such as fever, dyspnea and cough. Sudden olfactory loss can be diagnostic in this disease. Paranasal Sinus CT imaging, which is used to illuminate the pathophysiology of odor disorder in these patients, can be a new diagnostic tool for the clinician as a highly diagnostic method. For clear information on this subject, wider participation and multicenter research is needed.

Declarations

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Conflict of interest statement

No conflict of interest was declared by the authors.

Ethics

Ethics committee approval was received from Afyonkarahisar Healty Science University Clinical Research Ethic Committee.(11.05.2020-2020/5)

Approval of 05.05.2020 was obtained from the Ethics Committee of Afyonkarahisar Health Sciences University. Consent was not obtained from patients because it was a retrospective study.

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Tables

Table 1: Demographic and clinical characteristics of patients with COVID-19 with olfactory loss

COVID-19 Patients		
Gender		20 M/ 20 F
Mean Age (SD)	Total	47,58±20,57
	Male	46,00±22,56
	Female	49,18±18,81
Smoking (Y/N)		22/18 (%55-%45)
Clinical Finding	Fever	22 (%55)
	Headache	28 (%70)
	Cough	26 (%65)
	Dyspne	26(%65)
	Myalgia	19 (%47.5)
	Other	3 (%7.5)
Smell Loss	Mild Hyposmia	13/40 (%32,5)
	Moderate Hyposmia	13/40 (%32,5)
	Severe Hyposmia	9/40 (%12,5)
	Anosmia	5/40 (%10)
Severity of the disease	Mild	12(%30)
	Moderate	20(%50)
	Severe	8(%20)
PNS CT Finding (P/N)		2/27
Additional disease	No	12 (%30)
	Hypertension	11(%27.5)
	Asthma	1(%2.5)
	COPD	3(%7.5)
	Diabetes Mellitus	9(%21.5)
	Alzheimer	1(%2.5)
	Epilepsy	1(%2.5)
	Heart Failure	1(%2.5)
	Multiple sclerosis	1(%2.5)
Therapy	Enfluvir	36/40 (%90)
	Hydroxychloroquine	40/40 (%100)
	Azithromycin	6/40 (%15)
	Favipravir	3/40 (%7.5)
Intensive Care Requirement		3/40 (%7.5)
Exitus		3/40 (%7.5)

Table 2: Patients' degree of olfactory disorder and findings in the Paranasal Sinus CT

CCCRC Test Groups	Number of patients with COVID-19	CCCRC Test Score	PNS CT Finding Positive	p value
Normosmic	0/40 (%0)	6.00-7.00	0/0 (%0)	0,012
Mild Hyposmia	13/40 (%32,5)	5.00-5.75	0/13 (%0)	
Moderate Hyposmia	13/40 (%32,5)	4.00-4.75	0/13 (%0)	
Severe Hyposmia	9/40 (%22,5)	2.00-3.75	0/9 (%0)	
Anosmic	5/40 (%10)	0-1.75	2/5 (%20)	

Table 3: The relationship between severity of the disease and degree of olfactory disorder and Paranasal Sinus CT Findings

COVID-19 Disease Severity	Frequency (Percent)	CCCRC Test Score (Mean)	PNS CT Finding Rate(P/T)(Percent)	p value
Mild	12 (%30)	5,15±0,48	2/12 (%16,7)	p<0,05
Moderate	20 (%50)	3,93±1,09	8/20 (%40)	
Severe	8 (%20)	2,46±1,33	3/5 (%37,5)	

Figures

a



b



Figure 1

a, b: Paranasal Sinus CT Images of patients with olfactory loss: 2 patients with sudden loss of smell have soft tissue thickening at the entrance of both olfactory regions in Paranasal Sinus CT (indicated by the red arrow)