

## **Pediyatrik COVID-19 Olgularında Anozmi Prevalansı: 10.157 Çocuğun Deęerlendirilmesi (Çok Merkezli Çalışma)**

**Giriş-Amaç:** COVID-19 olgularında anozmi prevalansı çalışmalar arasında büyük farklılıklar göstermektedir. Günümüzde anozmi sıklığının yaş, cinsiyet, klinik şiddet gibi faktörlere ve farklı ülkeler ve etnik popülasyonlar arasındaki ilişkiye baęlı olarak nasıl deęiştiiğine dair net bir veri bulunmamaktadır. Bu çalışma ile ülkemizdeki COVID-19'lu çocuk olgularda anozmi prevalansını belirlemeyi ve koku farkındalık anketi ile objektif bir deęerlendirme yapmayı amaçladık.

**Materyal-Metod:** Bu çok merkezli prospektif kohort çalışmasına, Türkiye'nin 19 farklı şehrinde bulunan 37 merkez katıldı ve Ekim 2020 ile Mart 2021 tarihleri arasında başvuran olgular deęerlendirildi. Anozmisi olan olgularla başvuru sırasında ve hastalıktan bir ay sonra görüşme yapılması planlandı. Başvuru sırasında yapılan görüşmelerde yaş, cinsiyet ve COVID-19'a eşlik eden dięer semptomlar kaydedilerek COVID-19 klinik sınıflandırması yapıldı. Olgulara 20 sorudan oluşan koku farkındalığı anketi uygulandı ve bu anket bir ay sonra tekrarlandı. Ayrıca, anozmi süresi ve bir ay sonunda bulgularda düzelme olup olmadığı sorgulandı.

**Sonuçlar:** COVID-19 tanılı 10.157 olgunun 1266'sında anozmi saptandı ve prevalansı %12.5'di. Ancak; bazı hastaların verilerine ulaşılamadığından analiz 1053 hastada yapıldı. Anozmisi olan olguların 643'ü (%61.1) kız ve ortanca yaşları 190 (168-204) aydı. Anozmisi olmayanların ise %49.6'sı kız ve ortanca yaşları 176 (152-196) aydı (her iki karşılaştırma için  $p < 0.001$ ). Anozmi semptomlar başladıktan ortanca yedi (IQR: 3-14) gün sonra ortaya çıkmıştı. Anozmili vakaların 84'ünde (%8) anozmi tek semptomdu. Başlangıç zamanlarına göre 172 (%16.3) olguda genel semptomlardan önce, 341 (%32.4) olguda genel semptomlarla eş zamanlı, 456 (%43.3) olguda ise genel semptomlardan sonra anozmi saptandı. Bir ay sonra 88 (%8.4) olguda anozmi şikayetlerinde gerileme olmamıştı. Anozminin seyri klinik şiddet ile karşılaştırıldığında, hafif klinik şiddetteki olguların %7.7'sinde anozmi düzelmezken, orta/şiddetli/kritik klinik şiddetteki olgularda anozminin %13.3'ünde düzelmediği ve gruplar arasındaki farkın istatistiksel olarak anlamlı olduğu bulundu ( $p=0.04$ ).

**Tartışma-Sonuç:** Anozmi, COVID-19 olgularında sık görülen spesifik bir semptomdur ve bazı durumlarda tek semptom olabilmektedir. Çocuklarda ve ergenlerde anozminin prevalansı hakkında

sınırlı veri bulunmaktadır. Bu çalışma ile çocuklarda anozmi prevalansının erişkinlere göre daha düşük olduğu saptanmıştır.

**Anahtar Kelimeler:** Anozmi, COVID-19, çocuk, prevalans

# Prevalence of Anosmia in 10.157 Pediatric COVID-19 Cases

## Multicenter Study from Turkey

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**Introduction:** COVID-19-related anosmia is a remarkable and disease-specific finding. With this multicenter cohort study, we aimed to determine the prevalence of anosmia in pediatric cases with COVID-19 from Turkey and make an objective assessment with a smell awareness questionnaire.

**Material and Methods:** This multicenter prospective cohort study was conducted with pediatric infection clinics in 37 centers in 19 different cities of Turkey between October 2020 and March 2021. The symptoms of 10.157 COVID-19 cases 10–18 years old were examined. Age, gender, other accompanying symptoms, and clinical severity of the disease of cases with anosmia and ageusia included in the study were recorded. The cases were interviewed for the smell awareness questionnaire at admission and one month after the illness.

**Results:** Anosmia was present in 12.5% (1.266/10.157) of COVID-19 cases 10–18 years of age. The complete records of 1053 patients followed during the study period were analyzed. The most common symptoms accompany-

ing symptoms with anosmia were ageusia in 885 (84%) cases, fatigue in 534 cases (50.7%), and cough in 466 cases (44.3%). Anosmia was recorded as the only symptom in 84 (8%) of the cases. One month later, it was determined that anosmia persisted in 88 (8.4%) cases. In the smell awareness questionnaire, the score at admission was higher than the score one month later ( $P < 0.001$ ).

**Discussion:** With this study, we have provided the examination of a large case series across Turkey. Anosmia and ageusia are specific symptoms seen in cases of COVID-19. With the detection of these symptoms, it should be aimed to isolate COVID-19 cases in the early period and reduce the spread of the infection. Such studies are important because the course of COVID-19 in children differs from adults and there is limited data on the prevalence of anosmia.

**Key Words:** anosmia, ageusia, COVID-19, children

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COVID-19, caused by SARS-CoV-2, continues to spread rapidly around the world. Early detection and isolation of cases still remain important. While fever, cough, myalgia, and weakness are common symptoms of the disease, awareness has increased that anosmia and ageusia are specific findings.

In viral infections, anosmia may occur through the inflammatory reaction of the nasal mucosa and the development of rhinorrhea. However, many patients infected with SARS-CoV-2 experienced severe anosmia and ageusia without rhinorrhea or nasal congestion.<sup>1</sup> The pathophysiology of anosmia is thought to be sensorineural inflammation of the olfactory neuroepithelium.<sup>2</sup> Therefore, the anosmia seen in COVID-19 is a remarkable and disease-specific finding.

The prevalence of anosmia varies widely between studies. Currently, there is no clear data on how the frequency of anosmia changes depending on factors such as age, gender, clinical severity, and the relationship between different countries and ethnic populations. In this multicenter cohort study, we aimed to determine the prevalence of anosmia in pediatric cases with COVID-19 in our country and make an objective evaluation with a smell awareness questionnaire.

## MATERIAL AND METHODS

### Participants

This multicenter prospective cohort study was conducted between October 2020 and March 2021 with pediatric infection clinics from 37 centers located in 19 different cities of Turkey. Throughout the study period, cases 10–18 years old in whom SARS-CoV-2 was detected in respiratory samples by reverse transcriptase-polymerase chain reaction method were examined. It was planned to interview the cases with anosmia at admission and one month after the disease.

## Study Design and Definitions

During the interviews at admission, age, gender, and other symptoms accompanying COVID-19 were recorded. COVID-19 clinical classification was made (asymptomatic, mild, moderate, severe, critical). The smell awareness questionnaire consisting of 20 questions was applied to the cases with anosmia.<sup>3,4</sup> The questionnaire started with items that included awareness of smell and consisted of items that questioned smell acuity and smell-related behavioral characteristics. Afterward, the cases were informed that they would be called again one month later. One month later, the patients were interviewed by phone and the smell awareness questionnaire was applied for the second time. The answers to the questions were scored from 1 to 5. The responses were determined as follows, always (1 point), often (2 points), some time (3 points), rare (4 points), and never (5 points). In addition, the duration of anosmia, the onset time of anosmia, and whether there was any improvement in the findings at the end of one month were questioned. This study was approved by the Health Sciences University, Izmir Tepecik Training and Research Hospital Ethical Committee in accordance with the Helsinki Declaration (Decision number: 2020/14-70).

## Statistical Analysis

Statistical data were analyzed with IBM SPSS for Windows version 25.0 (Chicago, IL). Values for numerical variables were given as median (interquartile range) (IQR) or mean  $\pm$  standard deviation, depending on the normality distribution. Categorical variables were presented as numbers and percentages. Categorical variables were compared using the  $\chi^2$  test. Wilcoxon test was used to compare the questionnaires. A *P* value of  $<0.05$  was considered statistically significant for all predictions.

## RESULTS

### Characteristics of Participants With and Without Anosmia

Of the 10,157 patients with COVID-19, anosmia prevalence was determined 12.5% ( $n = 1266$ ). Two-hundred-thirteen patients who could not be contacted for various reasons or did not agree to participate in the study were excluded. The remaining 1053 cases were included in the study. Of the 1053 cases, 643 (61.1%) were female and the median age of the cases was 190 (168–204) months. When the cases were analyzed according to age groups, 34.9% were between the ages of 10–14 and 65.1% were between the ages of 15–18. When evaluated in terms of clinical severity, 925 (87.8%) were mild, 126 (12%) were moderate, one (0.1%) were severe, and one (0.1%) were critical.

Of the 10,157 COVID-19 cases in our population, 8891 (87.5%) had no anosmia. When the COVID-19 cases without anosmia were analyzed, it was found that 49.6% of them were female. Female gender was found to be significantly more common in cases with anosmia (61.1% vs. 49.6%,  $P < 0.001$ ). The median age of the cases without anosmia was 176 (152–196) months. When the cases were analyzed in terms of age groups, 52.3% were between the ages of 10–14 and 47.7% were between the ages of 15–18. It was observed that the cases with anosmia were older and the presence of anosmia was more common between the ages of 15–18 ( $P < 0.001$ ,  $P < 0.001$ , respectively). Clinical severity data were available for 8590 of the cases without anosmia. Of these cases 1322 (15.5%) were asymptomatic, 6604 (76.9%) were mild, 546 (6.4%) were moderate, 102 (1.2%) were severe, and 16 (0.2%) were critical clinical severity (Table 1).

### Clinical Characteristics of Participants with Anosmia

While ageusia was accompanying in 885 (84%) of the cases, fatigue in 534 (50.7%) cases, cough in 466 (44.3%) cases, headache in 456 (43.3%) cases, fever in 449 (42.6%) cases, myalgia in 433

**TABLE 1.** Characteristics of COVID-19 Patients Presenting With and Without Anosmia

	Patients with Anosmia ( $n = 1053$ )	Patients without Anosmia ( $n = 8891$ )
Age (months)*	190 (168–204)	176 (152–196)
Gender (female)**	643 (61.1)	4410 (49.6)
Clinical severity**		$n = 8590$
Asymptomatic	0 (0)	1322 (15.5)
Mild	925 (87.8)	6604 (76.9)
Moderate	126 (12)	546 (6.4)
Severe	1 (0.1)	102 (1.2)
Critical	1 (0.1)	16 (0.2)
Anosmia (days)*	7 (3–14)	
Onset of anosmia**		
As the only symptom of COVID-19	84 (8)	
Before general symptoms of COVID-19	172 (16.3)	
At the same time as general symptoms of COVID-19	341 (32.4)	
After general symptoms of COVID-19	456 (43.3)	
Outcome of anosmia**		
Regressed	965 (91.6)	
Not regressed	88 (8.4)	
Ageusia**	885 (84)	
Ageusia (days)*	7 (3–14)	
Onset of ageusia**		
As the only symptom of COVID-19 with anosmia	57 (6.4)	
Before general symptoms of COVID-19	173 (19.5)	
At the same time as general symptoms of COVID-19	261 (29.5)	
After general symptoms of COVID-19	394 (44.5)	
Outcome of ageusia at one month**		
Regressed	827 (93.4)	
Not regressed	58 (6.6)	

IQR, interquartile range.

\*median (IQR).

\*\**n*, %.

(41.1%) cases, and joint pain in 360 (34.2%) cases were other common symptoms. All symptoms and symptom durations of COVID-19 cases presenting with anosmia are shown in Table 2. When the duration of symptoms was examined, it was found that the median duration of anosmia was seven (IQR: 3–14) days. Anosmia was the only symptom in 84 (8%) of 1053 COVID-19 cases with anosmia. According to the onset times, anosmia was detected before general symptoms in 172 (16.3%) cases, concurrent with general symptoms in 341 (32.4%) cases, and after general symptoms in 456 (43.3%) cases. One month later, it was seen that there was no regression in the complaints of anosmia in 88 (8.4%) cases. The course of anosmia was compared with clinical severity. The cases were divided into two groups mild and moderate/severe/critical. While anosmia did not improve in 7.7% of cases in the mild clinical severity group, it was found that anosmia did not improve in 13.3% in the moderate/severe/critical clinical severity group and the difference between the groups was statistically significant ( $P = 0.04$ ).

### Clinical Characteristics of Participants with Ageusia

Ageusia was present in 885 (84%) of 1053 participants with anosmia. When the duration of symptoms was examined, it was found that the median duration of ageusia was seven (IQR: 3–14) days. Ageusia was detected before general symptoms

**TABLE 2.** Other Symptoms of COVID-19 Patients Presenting with Anosmia

Symptom	Symptom frequency (n, %)	Symptom duration (days) median (IQR)
Ageusia	885 (84)	7 (3–14)
Weakness	534 (50.7)	5 (3–7)
Cough	466 (44.3)	4 (3–7)
Headache	456 (43.3)	4 (2–7)
Fever	449 (42.6)	2 (1–3)
Myalgia	433 (41.1)	4 (3–7)
Joint pain	360 (34.2)	4 (2–7)
Appetite loss	272 (25.8)	5 (3–7)
Nasal congestion	239 (22.7)	4 (3–7)
Rhinorrhea	183 (17.4)	3 (2–6)
Chest pain	160 (15.2)	3 (2–7)
Nausea and vomiting	149 (14.2)	3 (2–5)
Dyspnea	145 (13.8)	4 (2–7)
Diarrhea	143 (13.6)	2 (2–4)
Stomach ache	110 (10.4)	3 (2–5)
Hoarseness	81 (7.7)	4 (3–6)
Tinnitus	28 (2.7)	3 (2–6)
Hearing loss	4 (0.4)	2 (2–3)

in 173 (19.5%) cases, simultaneously with general symptoms in 261 (29.5%) cases, and after general symptoms in 394 (44.5%) cases. One month later, it was seen that 58 (6.6%) patients did not regress in ageusia complaints (Table 1).

### Smell Awareness Questionnaire

While the median value of the total score of the questionnaire applied to the cases at the time of admission was 94 (IQR: 80–100) points, the median value of the total score of the questionnaire applied one month later was 46 (IQR: 31–62) points. All questions in the smell awareness questionnaire and the scores of the participants are shown in Table, Supplemental Digital Content 1; <http://links.lww.com/INF/E698>. A total of 20 questions and scores in the questionnaire were compared according to admission and one month after the illness. At the time of admission, the scoring was higher than the scoring one month later (94 vs. 46,  $P < 0.001$ ).

### DISCUSSION

With this study, we have provided the examination of a large case series across Turkey. Anosmia and ageusia are specific symptoms seen in cases with COVID-19. Given the current pandemic, it is thought that the chance of detecting the disease will increase in the presence of sudden onset anosmia and ageusia. The importance of this situation is understood day by day and precautions are taken. So much so that the American Academy of Otolaryngology-Head and Neck Surgery recommended that people with sudden anosmia and ageusia isolate themselves in the absence of other respiratory symptoms such as nasal congestion and rhinorrhea.<sup>5</sup> In countries where access to COVID-19 testing and resources are limited, these and similar recommendations are of great importance.

The prevalence of anosmia in COVID-19 patients varies widely between studies. In a systematic review of 27 publications that included a total of 19,424 COVID-19 patients, the prevalence of anosmia ranged from 4.23% to 98.33%.<sup>6</sup> In our population, this rate was 12.46%. In an international multicenter study of 394 cases of COVID-19 involving children and adults, the incidence of anosmia was significantly higher in cases in Germany and France than in China.<sup>7</sup> Age, regional variations, ethnic origin, and an insufficient number of cases in cross-sectional studies can be cited as the reasons for this variability.

In COVID-19 cases, anosmia is more common in women.<sup>8</sup> Similarly, female gender was detected more frequently in cases with anosmia in our study.

The exact pathophysiology of anosmia and ageusia in COVID-19 has not yet been fully elucidated. It mainly focuses on three mechanisms. First, it is thought that inflammation of the olfactory mucosa may be triggered by a viral infection of the nasal mucosa. Second is thought to be caused by damage resulting in inhibition of olfactory signal transduction. The third mechanism is that this neurotropic virus follows the olfactory pathway to attack the olfactory cortex of the brain's temporal lobe.<sup>9,10</sup> In a meta-analysis, in studies where SARS-CoV-2 negative patients were the control group, anosmia was more common in SARS-CoV-2 positive individuals.<sup>11</sup> This situation supports that anosmia has a specific place in COVID-19 disease.

While anosmia and ageusia due to nasal congestion or rhinorrhea are common in viral infections, the situation in COVID-19 is specific. Nasal congestion was detected in 22.7% of our cases, and rhinorrhea was found in 17.4%. This supports the hypothesis that different mechanisms are involved in COVID-19. In this study, in which we examined cases with anosmia and ageusia, the most common accompanying symptoms were fatigue (50.7%) and cough (44.3%). In a study examining the symptom profile of the disease for SARS-CoV-2 in the United Kingdom, the most common symptoms in school-age children were headache (62.2%) and fatigue (55.0%).<sup>12</sup> In the meta-analysis examining both community-based children and hospital admissions, fever (47%) and cough (42%) were reported as the most common symptoms.<sup>13</sup> Our population consisted of children with anosmia, although symptoms were similar to the COVID-19 case series.

The effects of symptoms accompanying anosmia on the severity, duration, and overall recovery rates of anosmia have been investigated in the literature. Patients with isolated anosmia have been found to have longer recovery times and more severe olfactory dysfunction than patients with anosmia accompanied by other clinical symptoms.<sup>8</sup> We did not make such a comparison in our study. In future studies, this situation can be handled and clearer results can be revealed.

In our population, non-permanent hearing loss developed in four (0.4%) cases. In the literature, cases in the adult age group with hearing loss after anosmia and ageusia have been reported.<sup>14</sup> In another study, hearing loss was found in 6.35% of COVID-19 cases.<sup>15</sup> The effect of COVID-19 disease on the auditory system still remains unclear. Therefore, it is necessary to be careful in terms of other sensory deficits in COVID-19 cases.

In our study, anosmia and ageusia were frequently observed after general symptoms (43.3% and 44.5%, respectively). Anosmia and ageusia were detected at a low rate as the only symptom in COVID-19 cases (8%, 6.4%, respectively). Similarly, in the literature, anosmia, and ageusia were observed as the sole symptom in 10% and after the general symptoms in 53%.<sup>7</sup> However, since the participants in our study were between the ages of 10–18, generalizing these rates to all COVID-19 cases may be misleading. Although anosmia and ageusia are specific symptoms, their detection late in the course of the disease can be seen as a disadvantage.

It has been reported that COVID-19-related anosmia is associated with a mild clinical course and a good prognosis. This mechanism is thought to help prevent both central neuroinvasion and viremia.<sup>16</sup> In our study, it was seen that 87% of the cases were in the mild clinic. A study of critically ill patients with COVID-19 in the intensive care unit supports the existing hypothesis that anosmia is less common with increasing disease severity.<sup>17</sup> On the other hand, in our cases with moderate/severe/critical clinical severity, we found that anosmia recovery rates were lower than mild. Based

on the available data, it can be said that anosmia is often associated with a mild clinical course, and recovery rates decrease with worsening clinical severity.

The recovery process and prognosis of patients with anosmia are of critical importance. Postviral anosmia shows complete or partial recovery in about two weeks to several months, depending on the pathophysiology of the anosmia.<sup>18</sup> In our cases, the median recovery times of anosmia and ageusia were seven days. In a study conducted with a large case series, the recovery time of anosmia was shorter in children than in adults.<sup>19</sup> With this result, it can be thought that restoring olfactory function occurs faster in children than in adults. The short-term improvement seen in our cases also supports our conclusion. One month later, when the cases were questioned again, it was observed that anosmia resolved with a rate of 91.6%. This high rate is promising to show that patients have a low risk of permanent dysfunction. Cases whose symptoms do not improve should be referred to otolaryngology clinics. As a matter of fact, a case of severe acute respiratory syndrome (SARS) associated with anosmia that has been ongoing for two years has been reported in the literature.<sup>20</sup>

There is no definitive treatment regimen for anosmia associated with COVID-19. The British Rhinological Society consensus guidelines recommend nasal/systemic steroid and omega-3 supplementation in addition to olfactory exercises.<sup>21</sup>

This study had some limitations. Initially, subjects were called for anosmia evaluation one month later; but the follow-ups thereafter were not included in the study. By evaluating long-term follow-ups, the relationship between COVID-19 and anosmia can be examined in depth. Second, a qualitative research method was used for anosmia assessment. The use of quantitative research methods can provide a more objective assessment.

In conclusion, anosmia and ageusia are common symptoms in COVID-19 and maybe the only symptom in some cases. With the detection of these symptoms, it should be aimed to isolate COVID-19 cases in the early period and reduce the spread of infection. There are limited data on the prevalence of anosmia in children and adolescents. Also, such studies are important because the course of COVID-19 in children differs from adults. We aimed to contribute to the literature in this sense with this multicenter study that included a large number of cases. It should be aimed to enrich the literature with similar studies that include long-term follow-up of the cases.

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