Uncommon Presentation of COVID-19 in Pediatric Patients: Anosmia

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Abstract

Objective The novel coronavirus disease 2019 (COVID-19) infection was declared as a pandemic by the World Health Organization on March 11, 2020. Although the complaint of anosmia is well described in adult patients, there is limited knowledge in pediatric patients. We aim to evaluate the epidemiological characteristics and clinical findings of children with anosmia in COVID-19-positive pediatric patients.

Methods Patients diagnosed with COVID-19 infection at 1 month to 18 years of age, who admitted to Meram Faculty of Medicine of Necmettin Erbakan University between March and June 2020, were retrospectively reviewed, and the patients who had anosmia or developed anosmia during follow-up were then included in the study. The diagnosis was established by polymerase chain reaction (PCR).

Results A total of 71 patients were diagnosed with COVID-19 and 14 (19.7%) of them had anosmia. Mean patient age was 14.07 (range: 10–16) years. Six of our 14 (42.8%) patients had anosmia at the time of diagnosis and anosmia developed in the follow-up among eight patients. The mean duration of anosmia in our patients was 6.9 ± 3.8 days. Recovery time was 1 to 4 days in four patients (28.5%), 5 to 8 days in four patients (28.5%), and 9 to 14 days in six patients (42.8%).

Conclusion In this article, it was emphasized that anosmia can be the sole manifestation or concomitant with other symptoms in children with COVID-19 disease. Care and attention is important to identify COVID-19 patients at an early stage of the disease and limit the spread of the virus.

Keywords
- anosmia
- COVID-19
- polymerase chain reaction
- children

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Introduction

A cluster of cases of severe pneumonia of unknown etiology emerged in Wuhan City of Hubei province in China in December 2019.[1] A new coronavirus, named severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was isolated from samples from the lower respiratory tract as the causative agent.[2] The current outbreak of infections with SARS-CoV-2 is termed as novel coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).[3] COVID-19 rapidly spread into at least 114 countries and killed more than 4,000 people by March 11, 2020, after which WHO officially declared COVID-19 as a pandemic on March 11, 2020.[4] In Turkey, 500,865 laboratory confirmed COVID-19 cases and 13,746 deaths have been reported up to November 30, 2020.[5] Overall, 14,388 cases in children under 15 years of age (7.3%) have been reported in Turkey up to June 28, 2020.[6]

Compared with adult patients, pediatric patients with COVID-19 infection are usually asymptomatic or present with mild symptoms such as fever; dry cough; fatigue; upper respiratory symptoms including nasal congestion and runny nose; and gastrointestinal symptoms including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea. Prognosis of infected children has been reported as favorable in the literature.[7,8] Anosmia is one of the clinical manifestations in COVID-19 infection and has been reported in adult population in the literature with limited data for children.[9–12] The aim of this study was to evaluate the epidemiological characteristics, as well as clinical findings of children with anosmia in COVID-19-positive pediatric patients.

Materials and Methods

This was an observational descriptive case series with retrospective study of pediatric patients (<18 years) who were admitted to the Emergency Department (ED) of the Meram Faculty of Medicine of Necmettin Erbakan University in Turkey between March and June 2020 with confirmed SARS-CoV-2 infection with the complaint of anosmia. The Meram Faculty of Medicine of Necmettin Erbakan University is a university hospital and was declared as a pandemic hospital after the first case of coronavirus in Turkey was identified in March 2020. Our hospital is a tertiary pandemic hospital where COVID-19 patients are followed-up as inpatients and outpatients and also referred from other hospitals. To prevent possible transmission during the pandemic period, a new outpatient clinic was set up in the emergency room where suspected cases were admitted. A separate follow-up system was established for polymerase chain reaction (PCR)-positive patients in our clinic. A follow-up form was filled in for inpatients during their hospitalization and daily follow-up was made by using telemedicine technique for outpatients. To monitor the COVID-19 pandemic and its impact on children, patients were followed for at least 14 days or, if symptoms were ongoing at 14 days, then they were followed-up as long as symptoms persisted. Demographic data, epidemiological history, complaints, physical examination, and therapies were recorded. Families were informed about the isolation measures at home and contact tracing was performed. Contact tracing is the process of scanning the contact chain for an infectious disease. The diagnosis of COVID-19 infection was established by PCR. During this time, nasal–throat swabs were taken from patients and then transferred to the Medical Molecular Laboratory of Meram Faculty of Medicine in a viral transport medium within 30 minutes. During this period, the samples that could not be delivered to the laboratory or could not be studied immediately were stored in the refrigerator at 2 to 8°C. First, manual extraction was performed for all samples in laboratory. Amplification process was performed by using COVID-19 quantitative (Q) reverse transcription-PCR (Bio-speedy, Istanbul, Turkey) kit on the resulting extract. Rotor gene-q (Qiagen, Germany) device was used, and the resulting amplification curves were monitored on the computer screen and then evaluated according to the criteria recommended by the kit manufacturer. This kit provides rapid diagnosis with real-time PCR in one step targeting the RNA-dependent RNA polymerase gene fragment. Our study obtained an ethics committee approval in accordance with the decisions numbered T09_42_13 by Ministry of Health and numbered 2020/2631 by Necmettin Erbakan University Meram Faculty of Medicine.

Pediatric patients who had a positive nasal PCR sample and had the complaint of anosmia or developed anosmia during follow-up were included in the study. The presence of anosmia was identified in the questionnaire. An objective test could not be used because of the pandemic period and so all patients were questioned subjectively about an osmia such as smelling onions or cologne. Azithromycin was given to all patients (5 mg/kg/day, periorally) for 5 days, in accordance with the algorithms specified by the ministry of health and 4 of 14 patients were treated with oseltamivir until influenza tests were concluded.

Responses to the survey were recorded in an electronic spread sheet. Anosmia was recorded as positive or negative. The overall results of this study were expressed as percentages for categorical variables, means ± standard deviation (SD) and as medians for continuous variables.

Results

A total of 71 pediatric patients were diagnosed with COVID-19 in this pandemic period and only 14 (19.7%) of them had the complaint of anosmia. Mean patient age was 14.07 (range: 10–16) years. Because the study was based on history taking and due to lack of an objective test, our youngest patient who could give a reliable history was 10 years of age. As anosmia could not be appropriately described in the younger age group, a 5-year-old patient who failed to give a reliable history was not included in the study. All patients included in the study had a history of contact with a known COVID-19-positive person, and six

Table 1 Summary of COVID-19 pediatric patients with anosmia

Patient ID	Age (y)	Sex	Additional complaints	Duration of anosmia (d)	Day of illness when anosmia was present (starting–finishing)	Family members with COVID-19	Anosmia history in family members
1	16	F	–	14	0–14	Mother, father	+
2	14	F	–	9	0–9	Mother, father	+
3	12	F	–	9	0–9	Mother, father	+
4	14	F	–	4	3–7	Brother in law	–
5	13	F	Fever	2	2–4	Mother, father, brother	+
6	16	F	Fever, cough	9	2–11	Mother, father, 2 brothers, sister	+
7	10	F	Fever, cough, fatigue	4	4–8	Mother, father	+
8	14	M	Fever, cough	5	6–11	Mother, father	+
9	12	M	–	5	2–7	Mother	+
10	16	F	Cough	11	0–11	Aunt	–
11	13	F	Fever, sore throat	14	2–16	Mother	+
12	16	M	Fever, fatigue	2	3–5	Aunt	–
13	15	F	Ageusia	6	0–6	Cousin	–
14	16	M	Cough, ageusia	6	0–6	Mother, father	+

Abbreviations: COVID-19, novel coronavirus 2019; F, female; M, male.

patients attended the emergency department at the onset of anosmia due to pandemic concerns. The complaint of anosmia was developed in the follow-up of eight patients and two of those patients had a contact history. The epidemiological factors, clinical findings, duration of anosmia, time of onset, and family history of anosmia are listed in ►**Table 1**.

Patients 1, 2, and 3 and patients 8 and 9 are siblings. It was noted that seven out of 14 patients had a family history of anosmia. The grandfathers of the patients' number 8 and 9 had died of COVID-19 infection. The mean duration of anosmia of our patients was 6.9 ± 3.8 days. Recovery time was 1 to 4 days in four patients (28.5%), 5 to 8 days in four patients (28.5%), and 9 to 14 days in six patients (42.8%). All patients were followed-up as an outpatient. All patients were cured without sequelae.

Discussion

Although anosmia is a well-defined clinical finding in adult patients with COVID-19, data in the literature for children is limited. There are only case reports in the literature in the English language.[9,10] Smell dysfunction is known to be common in viral infections. Several viruses can cause loss of smell via inflammatory reaction in nasal mucosa, leading to rhinorrhea. In a study of 24 patients with sudden onset of smell loss, 10 patients were evaluated with viral PCR analysis and only one patient tested positive for human coronavirus 229E.[13] In a multicenter study from 12 European hospitals 85.6% of 417 patients with COVID-19 had smell disorder, with 23.6% of patients with smell disorder also developing taste disorder during the pandemic period. The pathophysiology of anosmia still remains unknown but this finding is not related significantly to rhinorrhea or nasal congestion.[13,14] In another study, there was a significant association between COVID-19 and disorders of taste/smell, and chemosensorial disorder also was 10 times more common in SARS-CoV-2 positive patients.[15] In a study of COVID-19 patients, symptoms were particularly examined and 36.4% of patients had neurological symptoms. The symptoms were listed as disorders of central nervous system, peripheral nervous system, and muscle–skeletal system. The patients with peripheral nervous system disorders had complaints of hypogeusia (5.6%) and hyposmia (5.1%). Most of the neurological symptoms developed in the early term of the disease (mean duration was 1–2 days after admission to the hospital). The patients with no typical symptoms (fever, cough, anorexia, and diarrhea) of COVID-19 infection could only have neurological symptoms when admitted to hospital.[11] In patients with neurological symptoms at admission to hospital, COVID-19 infection should be considered as a cause and history must be taken carefully. Olfactory dysfunction developed before onset of other symptoms in 11.8% of cases in a multicenter adult study, in which it was found that 40% of the patients had anosmia at the time of diagnosis. In a multicenter study, the adult patients with anosmia had the following recovery times; 1 to 4 days in 20.3%, 5 to 8 days in 47.5%, 9 to 14 days in 28.8%, and more than 15 days in 3.4% of patients.[14] In our

study, the recovery time was 1 to 4 days in four patients (28.5%), 5 to 8 days in four patients (28.5%), and 9 to 14 days in six patients (42.8%), with no patients with a recovery time longer than 15 days. In a retrospective study with 326 adult patients with COVID-19, it has been showed that xerostomia, olfactory, and gustatory dysfunctions are common symptoms reported as concomitant and in some cases, the sole manifestation of COVID-19.[12] In our report, three patients had only anosmia and one patient had anosmia and ageusia as a manifestation.

Angiotensin-converting enzyme 2 (ACE-2) was determined as the functional receptor for SARS-COV-2 and the organs having this receptor are targeted.[16] Although the pathophysiology of anosmia in COVID-19 is still unknown, sensorineural inflammation of the olfactory neuroepithelium may play a more major role than conductive olfactory loss in causing anosmia, because it is possible that the virus may preferably target olfactory neurons in the upper respiratory tract.[9] The entrance receptor, known as ACE-2, is more predominantly found in nasal epithelial cells, particularly in goblet and ciliated cells.[17] It was demonstrated that virus enters the brain primarily via the olfactory bulb and the infection results in a rapid transneuronal spread to connected areas of the brain in a mouse model transgenic for ACE-2.[18] Anosmia in COVID-19 infection can be explained by this condition. In recent studies, it was suggested that ACE-2 could be specific to some populations and the level of expression in different tissues might be critical for the susceptibility to the symptoms and outcomes of COVID-19 infection.[19] The incidence of anosmia in COVID-19-positive family members of COVID-19 positive children was 71% (10/14) and this high rate was a notable point in our study, which may be linked to same ACE-2 gene polymorphism in family members.

Most publications that discussed treatment in children with COVID-19 suggested supportive treatment, including oxygen therapy and antibiotics for bacterial superinfections, while antiviral treatment is recommended by some researchers.[20] In our study, none of the children had an indication for hospitalization or supportive treatment. In terms of secondary bacterial infection, azithromycin treatment was given to all patients and oseltamivir was given as antiviral treatment until they have a negative influenza PCR result.

The limitations of the study are dependence on history taking for diagnosis of anosmia and lack of an objective test, the inability of young children to describe anosmia, and the small number of younger patients.

Conclusion

It is considered that the patients who neglect their anosmia spread the disease easily without knowing being infected, so that this symptom should be taken into consideration to detect the patients in early period. It is also important for source detection and prevention of dissemination of the pandemic COVID-19 infection. In this article, it was emphasized that anosmia can be the first manifestation of the COVID-19 infection in the pandemic period, so every child with isolated anosmia should be treated as a potential COVID-19 case.

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Conflict of Interest
None declared.

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