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Research Paper

Smell and Taste Dysfunction in Pediatric Patients With SARS-CoV-2 Infection

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ABSTRACT

Introduction: Anosmia and hypogeusia are frequent symptoms in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adults, but their incidence in children is unknown.
Objective: Describe the incidence and associated characteristics of olfactory and gustatory dysfunction in children with SARS-CoV-2 infection.
Material and methods: Descriptive study carried out by telephone survey of patients aged between five and 18 years with SARS-CoV-2 infection confirmed between March and December, 2020.
Results: Two hundred eighty Spanish patients (female: 42.2%) with a mean age of 10.4 years (±3.54, range: 5 to 17) were analyzed, 22.5% with other diseases (mostly respiratory: 11.8%). The most frequent symptoms were fever (55.36%) and neurological symptoms (45.7%). Forty-four (15.7%) were hospitalized due to the infection, in intensive care unit (ICU): 7.1%. Forty-five patients (16.1%) had anosmia and/or hypogeusia: 32 both, eight with hypogeusia only, and five with exclusively anosmia. The mean symptom duration in days for anosmia was 36.4, and for hypogeusia it was 27.6. Either symptom was the initial manifestation in 15 patients. None had anosmia/hypogeusia with no other symptoms. Anosmia/hypogeusia was related to the presence of respiratory infection, gastroenteritis, chills, odynophagia, myalgia, asthenia, and anorexia, but not severity (hospitalization/ICU admission). Cohabitation with another infected individual was associated with a higher incidence of anosmia/hypogeusia ($P = 0.041$) and duration of anosmia ($P = 0.006$). The presence of anosmia/hypogeusia in cohabitants was associated with longer duration of anosmia ($P < 0.001$).
Conclusions: The incidence of anosmia/hypogeusia in children with SARS-CoV-2 was lower than that reported in adults, although with a longer duration. Although no association was found between anosmia/hypogeusia and greater disease severity, recognition of these symptoms could help identify paucisymptomatic patients.

Introduction

Coronaviruses are enveloped single-stranded RNA viruses with a crownlike spike protein and belong to the family Coronaviridae (genus beta) within the subfamily Orthocoronavirinae. These viruses have significant genetic diversity and the ability to recombine. Coronaviruses can cause disease in humans and animals. There are seven coronaviruses known to cause infection in humans, categorized as alpha (229E and NL63) and beta (OC43 and HKU1, Middle East respiratory syndrome-related coronavirus, severe acute respiratory syndrome coronavirus [SARS-CoV], SARS-CoV-2).[1] The first coronaviruses were detected in the 1960s. On January 7, 2020, a new type of coronavirus was identified; its genome was sequenced on January 12, 2020, and the resulting disease was given the name coronavirus disease 2019 (COVID-19). The first case in Spain was declared on January 31 in La Gomera. On March 11, 2020, when confirmed cases had appeared in 114 countries, the World Health Organization declared a pandemic.[2]

Conflicts of interest: None.

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To invade human cells, SARS-CoV-2 employs the spike protein S1, which binds to angiotensin-converting enzyme 2, expressed mainly in the lungs and also in other organs.[3] At present, the most widely recognized form of initial transmission is from animals to humans with subsequent direct transmission between humans: by small droplets of Flügge, by aerosols, or by direct contact. The incubation period varies on average between three and seven days, although cases of weeks-long incubation have been described. It is accepted that transmission between asymptomatic subjects has been the main cause of the rapid spread of SARS-CoV-2. In the management of a health crisis, identification of paucisymptomatic patients is crucial to interrupt the potential person-to-person transmission chain of the virus.[4]

Neurological symptoms are common in SARS-CoV-2 infection in adults. One of the neurological symptoms identified as a hallmark of SARS-CoV-2 infection is hypogeusia and anosmia. In a Chinese series (n = 214) of patients with SARS-CoV-2 infection, 36.4% (78) of patients presented with neurological symptoms, including 9% hypogeusia or hyposmia.[5]

On March 17, 2020, the Spanish Society of Neurology was the first body of its kind to recommend that anosmia or hypogeusia be considered specific symptoms of the disease and advised 14 days of isolation for patients presenting these symptoms.[6] Subsequently, this manifestation of the disease has been corroborated in several studies in the adult population; as shown in Table 1,[4,7-13] the estimated incidence of this presenting symptom is between 19% and 85%.

In children, SARS-CoV-2 infection causes symptoms that are often less severe than in adults, although specific neurological disorders of childhood age have been also described. This neurological involvement in childhood has been poorly described, as has the incidence of symptoms such as anosmia and hypogeusia.[14]

Objective

The objectives of this study were to describe the frequency and features of olfactory and gustatory dysfunction in pediatric patients with SARS-CoV-2 infection acquired between March 2020 and December 2020 and to determine the presence of specific features or familial predispositions that may influence the presentation of these symptoms.

Material and Methods

A retrospective descriptive study was conducted of patients aged between 5 and 18 years with SARS-CoV-2 infection confirmed using one of the available diagnostic tests (i.e., rapid antigen test and polymerase chain reaction (PCR) on nasopharyngeal swabs, serology) between the months of March and December 2020. All patients were diagnosed at public infantile hospital of center of Madrid (Spain). A voluntary telephone questionnaire, through an interview with the researcher, was used to determine presence of qualitative smell or taste disorder, among other variables. The interview was conducted between one and nine months (mean 4 months) after infection. The following epidemiologic data and clinical outcomes were studied: age, sex, chronic underlying diseases, general and neurological symptoms, clinical outcomes, and symptoms in relatives.

First, we obtained the verbal consent of the parent and asked a filter question to establish whether the child was able to discriminate odors and tastes.

The following exclusion criteria were considered: adult age (>18 years), age less than five years, inability to report subjective symptoms (e.g., delayed overall development, language disorders), and patients with olfactory or gustatory dysfunction before the epidemic. The following inclusion criteria were set: pediatric patients aged between five and 18 years with laboratory-confirmed COVID-19 infection.

The Statistical Package for the Social Sciences for Windows (SPSS) was used to perform statistical analyses. Descriptive data were expressed as mean and S.D. Chi-square and Fisher exact tests were used to compare categorical variables, and the Student *t* test was used for continuous variables. A P value < 0.05 was considered statistically significant.

Results

Sample description

A total of 456 pediatric patients with a positive result from any of the available techniques for the detection of SARS-CoV-2 infection were initially selected. A total of 143 patients were excluded because they were younger than five years at the time of infection: 23 due to an inability to discriminate odors or flavors (10 childhood cerebral palsy, four epileptic encephalopathy, three autism spectrum disorder), one patient died, and one parent refused to participate. Eight patients were unreachable due to inaccuracies in their contact information.

Finally, 280 patients were analyzed (42.2% female, n = 118) with a mean age of 10.4 years (±3.54, 5 to 17) years. Of these individuals, 22.5% had an underlying comorbidity (11.8% respiratory, 8.6% neurological, 5% immunosuppression). The most frequent comorbidities were bronchitis/asthma. Other less frequent comorbidities were psychiatric disorders. A detailed description of the sample is provided in Table 2.

The diagnostic test used was PCR in 203 patients, antigenic rapid test in 28 patients, and serology testing in the remaining patients.

Sixty-three (22.5%) patients were asymptomatic, and the diagnosis was due to therapeutic intervention as elective surgery (n = 30) or after close contact with a patient with SARS-CoV-2 infection (n = 23, 8.21%).

TABLE 1.
Anosmia in the Adult Population With SARS-CoV-2 Infection[4,7-13]

Study	Methods	n	Anosmia	Female > Male	Dysgeusia Associated
Menni et al. [7]	Cross-sectional, community survey	579	59.4% (n = 344)	Yes	Yes
Lechien et al. [8]	Multicenter, questionnaire	417	85.6% (n = 357)	Yes	Yes
Vaira et al. [4]	Retrospective, self-reported	320	19.4% (n = 62)	Unknown	Yes
Spinato et al. [9]	Cross-sectional, telephone interview	202	64.4% (n = 130)	Yes	Yes
Yan et al. [10]	Retrospective, self-reported	169	75.7% (n = 128)	Unknown	Yes
Klopfenstein et al. [11]	Retrospective, self-reported	114	47% (n = 54)	Yes	Yes
Giacomelli et al. [12]	Cross-sectional, questionnaire	59	33.9% (n = 20)	Yes	Yes
Yan et al. [13]	Cross-sectional, self-reported	59	68% (n = 40)	Unknown	Yes

Abbreviation:
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

TABLE 2.
Sample Description

Characteristics	N (%)
Sex	
Female	118 (42.14)
Male	162 (57.86)
Underlying diseases	
Neurologic	24 (8.57)
Respiratory	33 (11.79)
Immunosuppression	14 (5)
Others	52 (18.6)
Symptoms	
Anosmia	
Frequency	38 (13.57)
Duration	36.4 days
Dysgeusia	
Frequency	41 (14.64)
Duration	27.6 days
Asymptomatic	63 (22.5)
Fever	155 (55.36)
Nasal obstruction	66 (23.57)
Cough	87 (31.07)
Dyspnea	18 (6.43)
Vomiting	47 (16.79)
Diarrhea	67 (23.93)
Abdominal pain	67 (23.93)
Odynophagia	64 (22.86)
Ocular discharge	21 (7.5)
Shaking, chills	37 (13.21)
General discomfort	90 (32.14)
Fatigue	122 (43.57)
Anorexia	66 (23.66)
Rash	33 (11.81)
Others (e.g., alopecia, cervicalgia,…)	17 (6.07)
Neurological symptoms	
Headaches	117 (41.78)
Dizziness	27 (9.64)
Myalgia	79 (28.21)
Others	20 (7.14)
Clinical diagnosis	
Acute gastroenteritis	64 (22.85)
Upper respiratory infection	96 (34.3)
Febrile syndrome with no apparent source of infection	38 (13.6)
Outcome	
Hospitalization	44 (15.71)
ICU admission	20 (7.14)
Relative	
Positive test	188 (67.1)
Anosmia or hypogeusia	99 (37.36)

Abbreviation:
ICU = Intensive care unit

The most frequent symptom of SARS-CoV-2 infection was fever (55.36%), followed by neurological symptoms (45.7%) such as headache (41.78%, n = 117), dizziness (9.64%, n = 27), or crisis (1.07%, n = 3). As for other symptoms, four were present in more than quarter of patients: general discomfort (32%, n = 90), cough (31%, n = 87), myalgia (28.2%, n = 79), and fatigue (43.6%, n = 122). Other less frequent symptoms are described in Table 2.

Forty-four patients (15.7%) were hospitalized due to infection, including 20 patients (7.1%) in the intensive care unit (ICU). Of these, 10 presented with pediatric inflammatory multisystem syndrome, four pneumonia, three septic shock, two thrombosis, and one bronchospasm.

Anosmia and hypogeusia in the sample

Forty-five of the 280 patients (16.1%) with confirmed SARS-CoV-2 infection reported anosmia or hypogeusia. Anosmia and hypogeusia presented in association in 72% of these cases (n = 33); eight patients presented with hypogeusia only and five with anosmia only (Fig).

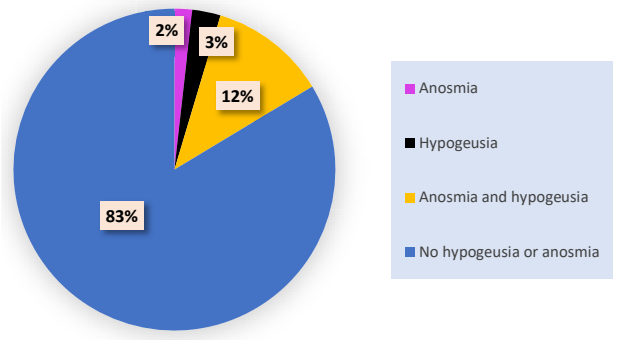

FIGURE. Anosmia and hypogeusia in the sample. The color version of this figure is available in the online edition.

Among the 38 (13.2%) patients with anosmia, the mean duration of the symptom was 36.4 days. Duration was ≥7 days for 31 patients and ≥14 days for 22 patients; at the end of follow-up the symptom had not resolved in five patients. Among the 41 (14.3%) patients with hypogeusia, the mean symptom duration was 27.6 days. The symptom persisted for ≥7 days in 30 patients and ≥14 days in 21 patients; four patients had not recovered by the end of follow-up.

Anosmia or hypogeusia was the initial symptom in 15 (5.4%) cases; in the rest, onset of either or both symptoms occurred 5.5 (±6.13, 1 to 31) days after the initial symptoms of the infection. None of the patients presented with anosmia or hypogeusia as an isolated symptom.

The relation between presence of hypogeusia and male sex was statistically significant ($P = 0.034$). A significantly higher probability of anosmia and hypogeusia at older age was found ($P < 0.05$).

We analyzed the relationships between the characteristics of the infection, individual features, and familial characteristics predisposing the children to infection. A statistically significant relationship was found between anosmia and signs and symptoms of upper respiratory tract infection such as fever ($P = 0.001$) and cough ($P = 0.004$), as well as chills ($P = 0.032$), odynophagia ($P = 0.001$), myalgia ($P = 0.001$), general discomfort ($P = 0.001$), and fatigue ($P = 0.001$). Presence of anosmia was not significantly related to dyspnea ($P = 0.243$); however, it should be noted that, among patients with anosmia, 10.81% had dyspnea compared with 5.76% of those without anosmia. The relationship between hypogeusia and the presence of acute gastroenteritis was statistically significant: diarrhea ($P = 0.003$) and abdominal pain ($P = 0.03$); other symptoms included fever ($P = 0.001$), cough ($P = 0.005$), chills ($P = 0.001$), odynophagia ($P = 0.001$), anorexia ($P = 0.002$), myalgia ($P = 0.001$), general discomfort ($P = 0.001$), and fatigue. However, these symptoms were not related to infection severity measured in terms of hospitalization (anosmia $P = 0.461$, hypogeusia $P = 0.347$) or admission to the ICU (anosmia $P = 0.807$, hypogeusia $P = 0.449$).

Only the presence of vomiting was significantly related to a longer duration of anosmia ($P = 0.0418$) (Tables 3 and 4).

The coexistence of a relative with SARS-CoV-2 infection was related to a higher incidence of anosmia/hypogeusia (80% vs 64.7%, $P = 0.041$) as well as a longer duration of olfactory impairment (40% vs 21%, $P = 0.006$). The presence of anosmia/hypogeusia in patients cohabitating with another infected person was related to a longer duration of anosmia in children (58.4% vs 21.95%, $P < 0.001$).

Discussion

Pathophysiology of olfactory and taste impairment in SARS-CoV-2 infection

Olfactory sensory neurons send chemical messages to the glomeruli of the olfactory bulb and later to the primary olfactory

TABLE 3.
Relationship Between Anosmia and Other Symptoms

Symptoms	Patients With Anosmia (%)	Patients Without Anosmia (%)	*P*
Fever	81.08	51.44	0.001
Fatigue	72.97	39.09	0.001
General discomfort	62.16	27.57	0.001
Myalgia	54.05	24.28	0.001
Cough	51.35	27.98	0.004
Odynophagia	48.65	18.93	0.001
Chills	24.32	11.52	0.032
Dyspnea	10.81	5.76	0.243

cortex, the limbic system, and hypothalamus.[15] Some studies suggest that SARS-CoV-2 can cause neurological manifestations through direct or indirect pathways.[5,16] Primary infection of non-neuronal cell types may be responsible for related alterations in odor perception in patients COVID-19 and suggests four possible mechanisms. First, local infection of vascular and supporting cells in the nose and bulb could cause significant inflammatory responses. Second, damage to supporting cells could indirectly influence olfactory sensory neuron signaling to the brain. Third, damage to the sustentacular cells and Bowman gland cells in mouse models can lead to the death of olfactory sensory neurons. Finally, vascular damage could cause hypoperfusion and inflammation, resulting in changes to the olfactory function of the bulb.[17-21]

Olfactory and taste impairment due to SARS-CoV-2 infection in adults

There is increasing evidence that olfactory and gustatory dysfunction is a prominent sign of SARS-CoV-2 infection, although the incidence may be underestimated.[22-24]

The incidence of anosmia in adult patients with COVID-19 varies widely among studies, with rates ranging from 19% to 86% with a greater incidence of these dysfunctions in women than in men (Table 1). Previous research has shown that individuals with smell disorders tend to have an impaired sense of taste.[4,7-13]

In a recent study of 357 adult patients, 85.6% had infection-related olfactory dysfunction and 88.8% reported gustatory disorders. There was a significant positive association between olfactory and gustatory dysfunctions ($P < 0.001$). Statistical analysis identified a significant association between fever and anosmia ($P = 0.014$). Similar results were found for gustatory dysfunction ($P = 0.001$, Mann-Whitney U test).[25]

In a retrospective observational study in the Nord Franche-Comté Hospital, which included 54 adult patients, the mean duration of anosmia was 8.9 (±6.3) days. Symptom duration was ≥7 days for 55% and ≥14 days for 20%, and one patient had not recovered at the end of the follow-up (28 days). Development of anosmia was 4.4 (±1.9) days after infection onset. Anosmia was associated with dysgeusia in 85% of cases.[11]

Olfactory and taste impairment in pediatric patients

There are limited data on the prevalence and characteristics of anosmia and ageusia in SARS-CoV-2 infection in children and teenagers, possibly due to the significantly milder clinical phenotype in these individuals. As a result, many cases of anosmia/hypogeusia may have not been diagnosed.

Smell or olfactory loss associated to SARS-CoV-2 infection is relatively uncommon in children.[26] In our study, 45 of the 280 patients (16.1%) with confirmed SARS-CoV-2 infection reported anosmia or hypogeusia. Anosmia and hypogeusia were associated in 72% of these cases (n = 33), and eight patients presented with hypogeusia only and five with anosmia only. There was a significant positive association between olfactory and gustatory dysfunction. These results are somewhat higher than the results of other pediatric studies, although the incidence is still lower than in adults.

In this sense, in the study by de Gaborieau et al. of 192 hospitalized pediatric patients (n = 157 with positive PCR and n = 35 with negative PCR but high suspicion of infection), 24 (12.5%) were admitted to the pediatric ICU. The median age was 1 year (42.7% female); 29.2% had an underlying condition (8.3% sickle cell disease, 5.2% asthma, and 4.7% immunocompromise), and the most frequent symptom was fever (n = 147, 76.6%). These authors described that 10 of these patients (5.2%) suffered anosmia or dysgeusia.[27]

In our study we found a statistically significant relation between the presence of hypogeusia and male sex ($P = 0.034$). Studies in adults have also found a higher prevalence in women.[7-9,11,12,28,29]

Risk of olfactory dysfunction increases with age.[30] We observe a statistically significant higher probability of anosmia and hypogeusia at older age in pediatric patients ($P < 0.05$).

Anosmia was significantly related to the presence of upper respiratory tract infection as evidenced by fever and cough and such other symptoms as chills, odynophagia, myalgia, general discomfort, and fatigue. Hypogeusia was significantly related to the presence of acute gastroenteritis (i.e., diarrhea, abdominal pain) as

TABLE 4.
Relationship Between Hypogeusia and Other Symptoms

Symptoms	Patients With Hypogeusiaypogeusia (%)	Patients Without otHypogeusia (%)	*P*
Fever	80	51.25	0.001
Fatigue	50	27.92	0.005
General discomfort	62.5	27.08	0.001
Myalgia	62.5	22.5	0.001
Cough	50	27.92	0.005
Anorexia	43.59	20.42	0.002
Odynophagia	47.5	18.75	0.001
Chills	30	10.42	0.001
Diarrhea	42.5	20.83	0.003
Abdominal pain	37.5	21.67	0.03
Dyspnea	12.5	5.42	0.091

well as other symptoms such as fever, cough, chills, odynophagia, anorexia, myalgia, general discomfort, and fatigue. In adults, this significant association has been seen between fever and anosmia. The presence of hypogeusia or anosmia associated with infection, and not only of the upper respiratory tract, suggests that this dysfunction may be due to inflammatory or vasculitic processes rather than a direct involvement of the mucous membrane.[31]

The mean duration of anosmia was 36.4 days and 27.6 days for hypogeusia. Regarding the duration of anosmia/hypogeusia, only the presence of vomiting was significantly related to a longer duration of anosmia ($P = 0.0418$).

Children are reported to have a milder clinical course with SARS-CoV-2 infection, but some will develop a severe form requiring ICU admission. The World Health Organization-China Joint Mission reported 2.5% severe cases in children younger than 19 years of which only 0.2% were critical cases.[32]

Hypogeusia and anosmia are rare in children, so presence of these symptoms may be specific enough to detect children with paucisymptomatic SARS-CoV-2 infection.[4,28]

In our study, presence of anosmia or hypogeusia was not related to severity of infection in terms of hospital or ICU admission; this has not been evaluated in other studies in children; in contrast, studies of the adult population have not only explored this relationship but also have examined the existence of a positive prognostic value.[28]

We observed that the coexistence of a relative with SARS-CoV-2 infection was related to a higher incidence of anosmia/hypogeusia (80% vs 64.7%, $P = 0.041$) as well as a longer duration of impaired sense of smell (40% vs 21%, $P = 0.006$); no previous studies have performed such an analysis. Also, we observed that the presence of anosmia/hypogeusia in patients cohabiting with other infected individuals was related to a longer duration of anosmia in children (58.4% vs 21.95%, $P < 0.001$). Although not studied previously, this relationship may point to a family-linked risk of greater taste or smell impairment owing to a possible genetic predisposition or inflammatory mechanisms.

Limitations

In our study we did not use objective tests to functionally measure taste or smell. We first asked parents or guardians of patients younger than five years a screening question to determine whether the patient was able to discriminate between odors and tastes. Most studies of odor identification in children have used tests designed for adults. There are numerous subjective and objective techniques to explore olfactory capacity, which depends on factors such as age, sex (hormonal variations), collaboration, culture (familiarity with certain smells), toxic habits, personal history, exposure time, and social aspects (associations between certain smells and situations).[33] The Pediatric Smell Wheel has been described as a powerful tool for testing olfaction in children as young as four years.[34] Although identifying smells requires a level of cognitive and linguistic sophistication, with the capacity to detect odors improving with the age and peaking during the third or fourth decade of life, many studies have found that although taste and smell vary depending on the individual, odor identification testing is viable from age three to five years.[35-38]

The second limitation is the retrospective study design used, conducting the interview up to nine months after infection, which could lead to the loss of data or the presence of imprecise data due to recall error.

Conclusions

In our patient series, 45 of the 280 children (16.1%) with confirmed SARS-CoV-2 infection reported anosmia or hypogeusia. Although less frequent than in adults, these symptoms presented a higher incidence than expected in the pediatric population due to viral infections, and the rate found here is slightly higher than that of other series of pediatric patients with SARS-CoV-2 infection. We found a higher predominance of the female sex, much like the results of studies in adults, and a statistically significant relationship between anosmia and hypogeusia.

In contrast to reports on adult patients, our series showed longer duration of anosmia and hypogeusia. In adults, a significant association has been observed between fever and anosmia, although in our series we have seen a significant association not only with fever but also with symptoms like chills, odynophagia, diarrhea, abdominal pain, anorexia, myalgia, general discomfort, and fatigue.

Nevertheless, vigilance and a high index of suspicion for anosmia and ageusia can facilitate early diagnosis and taking measures for self-quarantine, thus slowing the spread of the disease and helping us evaluate potential therapeutic approaches. The fact that this minor, uncommon, and nonspecific symptom may be the only indication of the disease cannot be overemphasized.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2022.07.006.

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