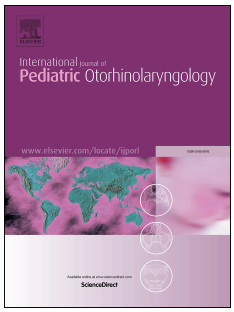
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Association of Anosmia and Neutralizing Antibody Production in Adolescents with SARS-CoV-2

Short Title: Relationship Between Anosmia and SARS-CoV-2 Antibody Production

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Abbreviations:

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

OGD: olfactory and gustatory dysfunction

SNOT-22: Sinonasal Outcome Test

Key Words:

SARS-CoV-2, Anosmia, Olfaction, Antibodies, SNOT-22

Text word count: 2311 words

Abstract

Background: To monitor olfactory/gustatory dysfunction and its relationship to SARS-CoV-2 IgG antibody responses in an adolescent population.

Methods: Adolescents with changes in olfactory/gustatory functions were enrolled in a 15-month study. The patients were evaluated with 1) SNOT-22, 2) pediatric smell wheel, and 3) SARS-CoV-2 antibody testing. The relationship between these scores and length of anosmia, and the amount of SARS-CoV-2 IgG antibodies were assessed. A brain MRI was performed in cases of persistent special sensory symptoms.

Results: Eighteen patients were identified with smell and/or taste complaints. Most of the patients were female (67%) and median age was 15 years (range 11-17). Twelve patients had prior SARS-CoV-2 PCR testing, with only five patients with a positive result. The median SNOT-22 score was 16 (range 0-52) and the median smell wheel score was 6.5 (range 1-11). Patients with taste difficulty were more likely to have a score less than eight. 78% of the patients tested positive for antibodies and there was a strong negative correlation between smell wheel score and antibody level (Spearman, ρ=-0.798, p=0.002). Five patients underwent MRI scan, and all resulted as normal olfactory bulb structures. 66% received nasal corticosteroids. 11 patients presented in follow up.

Conclusions: Adolescents presenting to a pediatric ENT clinic during the SARS-CoV-2 pandemic were likely to have prolonged (>6 weeks) symptoms of SARS-CoV-2. The majority do not report positive PCR testing result but do report systemic symptoms including anosmia. This suggests that anosmia may be both a late and prolonged symptom of SARS-CoV-2.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic still looms large as infections continue to increase at peak rates. The threats of novel variants of the virus, such as the Delta and Omicron, are concerning for breakthrough infections and antibody resistance, despite increasing rates of vaccination and natural immunity [1]. SARS-CoV-2 infection has a variety of clinical manifestations, including olfactory and gustatory dysfunction (OGD). Multiple studies report a range of prevalence of anosmia or dysgeusia from 31% to 67% of adult patients [2-4]. Moreover, in pediatric patients the range of smell alterations is 1% to 68% and 0% to 24% for taste alterations [5,6]. Additionally, olfactory and gustatory function recover quicker in pediatric patients than in adult patients [7,8], highlighting the importance of studying OGD in pediatric patients to better understand the symptom course.

Considering emerging variants, antibody production and their efficacy against SARS-CoV-2 remain important factors in the manifestation of OGD. Currently, most studies highlight the immune response's relation to OGD in adult populations only. In one study, 57.4% of adult patients with anosmia tested positive for IgG antibodies while another study showed that 80% of anosmia patients produced neutralizing antibodies [9,10]. In addition, the first study found that patients expressing anosmia or dysgeusia were 5.23 and 4.99 times more likely, respectively, to test positive for antibodies than patients not expressing these symptoms. Interestingly, viral load and SARS-CoV-2 IgG positivity were not associated with OGD presence, severity, or recovery [11,12]. These findings point to the need for increased research on individual factors rather than viral load and antibody activity for OGD in SARS-CoV-2 infection. An emphasis on studying antibody production in pediatric in relation to OGD offers a promising outlet for characterizing the immune response.

In this study, we examined OGD and its relationship to IgG antibody responses in an adolescent population. In our analysis, we aimed to capture the clinical course of OGD, including length of symptom presentation and recovery time. We hypothesized that symptom severity was one factor that impacts the strength of anti–SARS-CoV-2 IgG antibody response.

Materials and Methods

The present observational cohort study was conducted at the Otolaryngology Department of Children's National Medical Center in Washington, DC, after being approved by the institutional review board (reference ID: Pro00016404). We evaluated the olfactory and gustatory dysfunction in adolescent SARS-CoV-2 patients from March 2020 to July 2021. The inclusion criteria were adolescents, aged 12 to 17 years, who presented to the ENT clinic with perceived changes in smell or taste. All patients meeting the inclusion criteria were systematically evaluated with the 22-item Sinonasal Outcome Test (SNOT-22), pediatric smell wheel, and SARS-CoV-2 IgG testing (DiaSorin Liaison XL SARS-CoV-2 immunoglobulin G (IgG) S1/S2 assay). SNOT-22 is a validated patient-reported outcome measure to assess sinonasal symptoms. The pediatric smell wheel is also a validated patient-reported outcome measure that assesses olfactory function through the identification of 11 different odors (scents of onion, soap, popcorn, bubblegum, banana, cherry, rose, chocolate, smoke, peppermint and cinnamon). When applicable, patients were treated with steroids, zinc, and smell retraining, and observed with follow up MRI in cases of persistent symptoms. Patient age, gender, ethnicity, and prior SARS-CoV-2 PCR testing were collected at initial presentation. The duration of loss of smell and/or taste was noted in a follow up ENT consultation.

The statistical analysis was performed with R software (R Core Team 2022, version 4.1.2). Categorical variables are reported in numerals and percentages of the total. Descriptive statistics

for quantitative variables are given as the median (range). A non-parametric spearman correlation was conducted to determine the relationship between SNOT-22 score, smell wheel score, and length of anosmia, and the amount of SARS-CoV-2 IgG antibodies. A *p* value of less than .05 was considered statistically significant.

Results

Eighteen adolescent patients were enrolled in this study (Table 1). The cohort had a median age of 15 years old (12-17), with 12 females (66.7%) and six males (33.3%) (2:1). Nine (50%) patients identified as Latino, six (33.3%) identified as African-American, two identified as Caucasian (11.1%), and one (5.6%) patient did not specify (Table 2). Olfactory and gustatory symptoms included 12 (66.7%) patients with anosmia, 11 (61.1%) patients with dysgeusia, three (16.7%) patients with hyposmia, and three (16.7%) patients with parosmia.

Among the 18 participants, 12 (66.7%) had reported a prior SARS-CoV-2 PCR test with 5 (58.3%) reporting a positive result. At their initial visit, patients had been experiencing olfactory symptoms for a median of five months (2 weeks – 1 year). The median SNOT-22 score was 16 (0-52). The SNOT-22 categories with the highest scores were decreased sense of smell or taste, feelings of frustration, sadness, and irritability, nasal issues such as blockage or runny nose, and sleep issues including difficulty falling asleep and tiredness. The median smell wheel score was 6.5, (range 1-11) (Table 3). Patients with taste difficulty were more likely to have a score less than 8. Five (27.8%) patients had an MRI scan and two (11.1%) patients had a CT scan. All MRI scans showed normal olfactory bulb structures. Both CT scans showed no cause of olfactory dysfunction.

At the time of sample collection, none of the patients had received the SARS-CoV-2 vaccine. 15 (83.3%) patients had SARS-CoV-2-IgG antibody testing when they presented at their initial visit, and 14 (93.3%) of those had a positive test result. Of those who tested positive for SARS-CoV-2-IgG antibodies, seven patients (50.0%) had a level enough for neutralizing ability (≥ 80 AU/mL) and seven patients (50.0%) had below neutralizing levels (<80 AU/mL). The median level of antibody for patients above the neutralizing cutoff was 113 AU/mL (81.3 - >400) and the median level of antibody for patients below the neutralizing cutoff was 61 AU/mL (33.3 – 77.3) (Table 4). Out of the 14 patients who tested positive for SARSCoV2 IgG antibodies, 11 (71.4%) patients either had a previous negative PCR test (6) or did not have a PCR test (5) (Figure 1). A spearman correlation found a significant negative correlation of 0.798 (p=0.002) between smell wheel score and antibody level (Figure 2). However, both length of symptom presentation and SNOT-22 score were not correlated with antibody levels (ρ=-0.134, p=0.663 and ρ=-0.341 (p=0.254), respectively).

All patients were provided with smell retraining. 13 (72.2%) patients were given nasal corticosteroids. Patients with dysgeusia were ordered zinc. 11 (61.1%) patients presented for a follow up visit. After ENT interventions, seven (38.9%) patients report some improvement in olfactory function and three of those seven patients (42.9%) reported that they gained some sense of smell, however, were also experiencing parosmia.

Discussion

In this study, we evaluated 18 adolescent patients with persistent SARS-CoV-2 related olfactory dysfunction. Our study population is unique in that most of them had already tested negative for SARS-CoV-2 infection on a PCR test, yet they still had SARS-CoV-2 IgG

antibodies. This suggests that at the time of the PCR test the patients did not have active infection, however, they were still experiencing symptoms.

Initially, our patients had seen their primary care provider for treatment of OGD, and still their symptoms persisted. We observed that olfactory dysfunction lasted for 2 weeks to 1 year, with a median of 5 months. The persistence of anosmia in these patients is exceptionally long and raises some implications. First, multiple studies reported that chemosensory loss in SARS-CoV-2 adult patients recovers in about 1–2 weeks of onset, pointing to non-neural epithelial cells on the olfactory epithelium as infection targets [16]. Many studies found that the majority of SARS-CoV-2 induced anosmia is an early symptom such as the study by Vaira et al., which found that in their population smell impairment was the first symptom in 18.1% of patients and a majority of the patients had a short clinical course [12]. However, in the same study 34% of patients had persistent olfactory symptoms. This finding is similar to multiple other studies that characterized late and prolonged anosmia as a common symptom in SARS-CoV-2 “long haulers.” One study highlighted that a potential cause of continued olfactory dysfunction could be persistent degeneration of receptors in the olfactory epithelium after infection with SARS-CoV-2 or poor recovery in the olfactory epithelium [21]. The improved olfactory function seen in our patients after smell retraining and nasal corticosteroids supports this hypothesis. Moreover, five patients received MRI due to very long cases of anosmia. In all five cases there were no structural abnormalities to the olfactory bulb which is in accordance with the findings of both Checchini et al. and Galougahi et al. who observed an absence in structural abnormalities in the olfactory bulb through MRI [17,18]. Further work-up is necessary to elucidate the cause of OGD in this adolescent population.

In addition, Zhu et al. showed that 31.7% of patients in their study had olfactory dysfunction in prolonged infection while Graham et al. had 55% of patients with olfactory dysfunction in prolonged infection [22, 23]. Further, Zhu observed that olfactory function at 18 weeks was higher than at 14 weeks, marking a similar improvement that we witnessed in our study [23]. Similarly, a study conducted in children found that although only 1.8% of the participants experienced prolonged symptoms, the most common symptom in prolonged infection was anosmia [24]. Based on this, we suggest that anosmia may be a late and prolonged symptom of SARS-CoV-2 infection in some adolescent cases.

Of the patients that received SARS-CoV-2 IgG antibody testing, only one tested negative for antibodies. The patient had a family history of Hashimoto's disease and laboratory work-up found that they had subclinical hypothyroidism. At the initial ENT visit, the patient's main concerns were nasal blockage, facial pain, decreased smell, difficulty falling asleep, and waking up feeling tired. The patient had a normal CT scan of paranasal sinuses and negative allergy testing. The patient was given a nasal corticosteroid and at follow up their sense of smell was improved. Due to a negative allergy test and a negative antibody test, environmental and viral causes of anosmia were ruled out. Furthermore, based on the clinical link between hypothyroidism and decreased olfactory function, this patient's anosmia was most likely due to underlying thyroid deficiency as opposed to an infectious etiology [25,26,27].

Our results demonstrated that worse smell wheel scores significantly correlated with increased levels of antibody present. Cervia et al. found an inverse correlation between the levels of nasal antibody levels and severity of SARS-CoV-2 infection [13]. On the other hand, another study found that SARS-CoV-2 antibodies bind and block human olfactory receptors and can cause reversible anosmia observed in our patients [14]. Further, typically SARS-CoV-2 infection

severity correlates with more potent SARS-CoV-2 neutralizing antibody response [15]. Our findings support the two latter claims due to the characteristics of the patients' anosmia and the observed correlation with olfactory function and antibody level.

Our study has some limitations. One limitation is the small sample size, which limits the significance of statistical tests and prevents the analysis of relationships between some variables. For example, we were able to find a statistically significant relationship between smell wheel score and antibody level despite the small sample size. However, the decrease in statistical power prohibited us from detecting a relationship between length of symptom presentation and SNOT-22 score and antibody levels that we would otherwise have expected in a larger sample based on the similar purpose of all three variables. Thus, the small sample size and narrow age range makes it difficult for our study to be generalized across a broader population.

Another limitation is the patients did not receive the same treatment. While all patients initially presented in the same way, and all patients received smell retraining, not every patient was given nasal corticosteroids or other treatments. This prevents us from comparing a before and after treatment, making it difficult to determine the effectiveness of treatment options. In relation to this, another limitation is the lack of a control group. Again, this prevents us from making comparisons between treatments as well as between the three olfactory variables. Additionally, we used patient-reported details of their olfactory symptoms which could lead to potential biases.

However, a strength of our study is that we used validated psychophysical olfactory tests to empirically characterize patient's olfactory symptoms. Also, our study was racially diverse allowing for some generalizability. Lastly, by detecting SARS-CoV-2 IgG antibodies we obtained a more accurate antibody measurement.

In order to improve this study for the future multiple adjustments in our methods must be made. Firstly, recruitment of a larger patient population must be done to ensure the validity and accuracy of conclusions from the data. Secondly, the study should divide patients into groups based on the treatment they have received so that there can be a proper comparison between the effectiveness of treatment options for olfactory dysfunction. Lastly, there should be a standardized protocol where each patient is evaluated initially and after treatment so that further conclusions can be made about the efficacy of treatments.so that further conclusions can be made about the efficacy of treatments.

Based on this study, there are other related research questions that should be pursued. With increasing rates of vaccination among children, it will be interesting to know if rates of anosmia decreased as well as the severity as may be expected. Another question is if MRI is useful during diagnostic work up for children who present with anosmia due to SARS-CoV-2. Moreover, research focused on the social and emotional effects of anosmia in children is necessary to determine the complete impact of SARS-CoV-2 infection.

Conclusion

This current study is one of few studies to characterize adolescent patients with SARS-CoV-2 related anosmia. The study contributes to more appropriate patient management by demonstrating the course of olfactory dysfunction in prolonged cases. Further, we demonstrate that SARS-CoV-2 IgG antibody level may be an indicator for the severity of olfactory dysfunction. Additionally, based on our MRI findings we suggest that it may be prudent to delay obtaining MRI for isolated anosmia during the SARs-CoV-2 pandemic. Most of the patients report systemic symptoms including anosmia, and therefore we suggest anosmia may be a late

and prolonged symptom of SARS-CoV-2 in some cases. Our study can guide clinicians in best-practices for the care of adolescent with persistent smell and taste complaints.

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Table 1. Individual Patient Characteristics

Age	Sex	Ethnicity	Reported SARS-CoV-2 Symptoms	Dysgeusia (Y/N)	Length of Symptoms	Results of PCR Test	SNOT-22 Score	Smell Wheel Score	Imaging (Y/N)	Antibody Test Result	Antibody Level (AU/mL)	Given Nasal Corticosteroids (Y/N)	Reported SARS-CoV-2 Symptoms at Follow Up
14	M	Hispanic/Latino	decreased sense of smell, altered taste	Y	5 months	Negative	4	10/11	Not Performed	No Test	No Test	Y	Sense of smell improved but is altered and now everything smells bad.
16	F	Black/African American	decreased sense of taste and smell	Y	2 weeks	Positive	16	6/11	MRI	Positive	97.9	N	Smell returned 40% after 6 months with smell retraining but smell bad
17	M	Black/African American	loss of taste and smell	Y	4 months	Negative	Not Reported	3/11 and 5/11 at f/u	Not Performed	Positive	195	Y	No improvement in smell
15	F	Hispanic/Latino	loss of taste and smell	N	9 months	Positive	26	6/11	CT Scan	No Test	No Test	Y	Smell has been inconsistent but no improvement in smell
16	F	Black/African American	loss of smell, altered taste	Y	9 months	Negative	7/11 for SNOT-11	Not Reported	Not Performed	Positive	76.6	Y	Smell is slowly coming back
17	F	Black/African American	Altered smell	N	5 months	No Test	0	1/11	Not Performed	Positive	207	N	Did not follow up
14	M	Hispanic/Latino	loss of taste and smell	Y	4 months	Negative	14	9/11	Not Performed	Positive	61	Y	Did not follow up
17	F	Hispanic/Latino	altered smell and taste	Y	Not Reported	No Test	52	9/11	MRI	Positive	33.7	Y	small improvement in smell and taste, SNOT-22 of 43 at follow up
17	F	Hispanic/Latino	loss of smell	N	Not Reported	Positive	16	11/11	MRI	Positive	60.3	Y	No improvement in smell
13	F	Caucasian	loss of smell	N	6 months	Negative	30	3/11	Not Performed	Positive	101	N	Did not follow up
15	F	Caucasian	loss of smell	N	12 months	No Test	31	Not Reported	CT Scan	Negative	<3.8	Y	No improvement in smell
14	F	Hispanic/Latino	decreased smell	N	4 months	No Test	46	8/11	Not Performed	Positive	77.3	Y	Did not follow up
14	F	Black/African American	loss of smell, altered taste	Y	6 months	Negative	4	4/11	Not Performed	Positive	81.3	Y	Did not follow up
12	F	Hispanic/Latino	loss of smell	N	Not Reported	No Test	22	Not Reported	Not Performed	No Test	No Test	N	Did not follow up
16	M	Hispanic/Latino	altered in taste when eating meat	Y	2 months	Positive	Not Reported	Not Reported	MRI	Positive	45.6	N	Taste is returning slowly
11	M	Black or African American	decreased smell and test	Y	4 months	No Test	15	7/11	Not Performed	Positive	>400	Y	Did not follow up
14	M	Did Not Specify	loss of smell and taste	Y	6 months	Negative	6	8/11 to 12/12 on f/u	Not Performed	Positive	73.2	Y	No improvement in smell
17	F	Hispanic/Latino	altered smell and taste	Y	3 months	ositive	18	5/11	MRI	Positive	113	N	Improvement in smell, SNOT-22 is 29 and smell wheel 7/11 at follow up

Table 2. Patient Demographic Summary

Gender	
Male	6 (33.3%)
Female	12 (66.7%)
Age (Years), Median (Range)	15 (12-17)
Race/Ethnicity	
Latino/Hispanic	9 (50.0%)
Black or African American	6 (33.3%)
Caucasian	2 (11.1%)
Other	1 (5.6%)

Table 3. Patient Olfactory Function

Olfactory and Gustatory Symptoms	
Anosmia	12 (66.7%)
Hyposmia	3 (33.3%)
Parosmia	3 (33.3%)
Dysgeusia	11 (61.1%)
Length of Olfactory Symptoms (Months), Median (Range)	5 (0.5-12)
Olfactory Function, Median (Range)	
SNOT-22	16 (0-52)
Smell Wheel (Out of 11)	6.5 (1-11)

Table 4. Patient SARS-CoV-2 IgG Antibody Levels

Antibody Group	
Neutralizing	7 (50.0%)
Below Neutralizing	7 (50.0%)
Amount of Antibody, Median (Range)	
Neutralizing	113 (81.3 - >400)
Below Neutralizing	61 (33.3 – 77.3)

Figure 1. Flow Diagram of Patient Antibody Testing Results

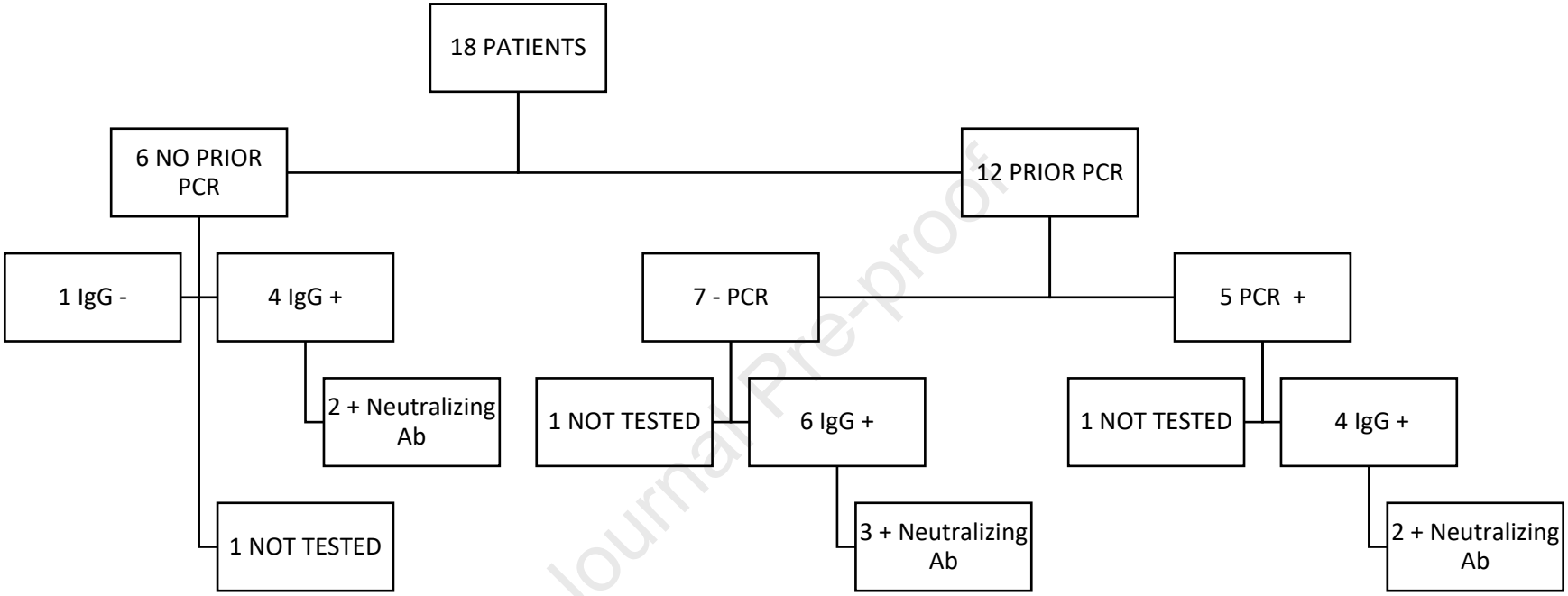

Figure 2. Correlation Between Smell Wheel Score and Antibody Level