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Subtle olfactory dysfunction after SARS-CoV-2 virus infection in children☆

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ABSTRACT

Objectives: Anosmia/hyposomia have been described as early signs of COVID-19 infection in adults, including young asymptomatic patients who commonly refer olfactory disfunction as their only clinical manifestation. Very few studies involving paediatric age patients have been published until now. This study aims to determine the presence of olfactory dysfunction in children with COVID-19 infection through the use of a self-reported questionnaire and a new olfactory screening tool.

Methods: Nested case-control study. All paediatric patients screened by reverse transcription polymerase chain reaction (RT-PCR) and Anti-SARS-CoV-2 antibodies for COVID-19 infection, during the study period (March–May 2020), were asked to respond to a questionnaire about symptoms of olfactory disfunction. Patients above six years old also performed an odor identification test based on seven odorants (Kradeo®). This test was designed based on our cultural context and eating habits.

Results: 126 patients were recruited, including 33 with COVID-19 infection. 15% of the infected children referred anosmia and/or dysgeusia on the questionnaire, all of them were older than eleven years. The results of the odor test (69 patients) revealed subtle disturbances in the infected group (mostly misrecognition of odorants). Median odorant recognition was 3 odors [Interquartile range (IQR) 2–4] in case group and 4 [IQR 3–5] in controls. Male patients showed significantly larger disturbances than girls in both groups ($p = 0.03$).

Conclusion: Self-referred prevalence of olfactory disfunction in our sample of infected children is lower than that described in adults, especially among the youngest ones, maybe due to immature development of angiotensin-converting enzyme 2 (ACE2) receptors expressed in nasal mucosa. Nevertheless, one month after infection, subtle disturbances (misrecognition of odors) were identified among the infected children. This screening olfactory test provides a hygienic, user-friendly tool, suitable for screening children older than six years of age.

1. Introduction

After some early, anecdotal reports from China, a variety of international studies have described a wide range of loss of smell in COVID-19 adult patients [1,2]. In one European study, 85.6% of patients reported olfactory dysfunction and this symptom appeared before other symptoms in 11.8% of cases, usually showing a sudden onset [3]. Sensorineural inflammation of the olfactory neuroepithelium may play a larger role than conductive olfactory loss in causing anosmia in these patients [4]. Asymptomatic infected young adults may show osmic disturbances as their only symptom [5,6].

Based on these prior findings, it is reasonable to expect children, who are mostly paucisymptomatic patients in this pandemic, to have a significant rate of osmic anomalies. However, comprehensive studies involving paediatric populations are still lacking. In a recent metanalysis published by Tong [2] only a few patients, enrolled in the 10 studies compiled in the review (n = 1627), were younger than 15 years. Anecdotical reports account for most paediatric age knowledge about osmic disturbances [7]. Mak et al. presented three clinical cases of adolescent age [8]. All paediatric data were based on clinical records and/or self-reports, with the inconvenience of the subjective nature of smell sensation that makes objective assessment difficult, especially in

☆ The authors confirm that no prior presentation of the study data as an abstract or poster has taken place.

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younger children. A systematic evaluation using a sniffing test in young children with COVID-19 infection is urgently needed. The only experiences with olfactory tests and COVID-19 infection that have been previously reported are restricted to adults [9,10].

This study aims to quantify the prevalence of olfactory disfunction in a paediatric population exposed to COVID-19 infection and to evaluate olfactory disfunction through the use of a novel olfactory screening test (Kradeo®) that has been designed to incorporate easily recognizable smells and is safe to implement during the pandemic.

2. Material and methods

A nested case-control study within an ambispective cohort study was conducted in a single-center, university tertiary-care hospital. The study was approved by the Regional Ethics Committee.

Patient selection: all paediatric patients (0–15 years) with clinical suspicion of COVID-19 infection that had been screened by SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) were invited to join the study. They were enrolled in the study after their parents or legal tutors signed an informed consent. A dual consent procedure, including both child's assent as well as parents' consent, was done from the age of twelve.

Study period: 3 months, March–May 2020.

Study protocol: After recovery from infection and at least 21 days after RT-PCR test, all patients who met the inclusion criteria completed a questionnaire about olfactory and taste disturbances and other clinical symptoms experienced during their illness, as well as a blood test to detect the presence of anti-SARS-CoV-2 ELISA Immunoglobulin G (IgG) (EUROINMUN®). Children above the age of 6 were also asked to perform a screening test to monitor their olfactory function (Kradeo®).

Patients were divided into two groups based on microbiological results, infected and not infected by the virus. Cases were considered when a positive result for RT-PCR and/or Anti-SARS-CoV-2 ELISA IgG was achieved.

Odor identification test: we employed a 7-odorant identification test (Kradeo®). The test was designed for the clinical assessment of olfaction based on the identification of familiar odorants, selected according to our cultural context and eating habits.

Odorants were labelled with a correlative letter: jasmine (A), mint, (C) anise (D), vinegar (E), cinnamon (F) and lemon (G). A neutral odor (no odor) was added (B).

Odorants belonged to different olfactory families (floral, citrus, etc). Five of them were used to evaluate the purely olfactory stimulus through the first cranial nerve or olfactory nerve (jasmine, mint, anise, cinnamon and lemon). In addition to this, vinegar (acetic acid) was used to also evaluate the somatosensorial component of olfaction, executed through the fifth paired cranial nerve or trigeminal, and thus the ability to show a reflex response to a situation of potential danger.

Every odor was sniffed from separate paper strips that had been impregnated with a concentrated odor essence and packaged in individual single-use vacuum sealed plastic envelopes to avoid contagion. Envelopes were opened, one by one, just immediately before the test started. The child sniffed the odorants sequentially with a bilateral inhalation procedure (2 cm away from their nose). A resting interval of 15–20 s was imposed between the sampling of each odorant. The whole test required about 5 min to be completed.

Answers were recorded and classified as follows: 1 = perfect match, when the odor was clearly recognised by the child, 2 = quite approximate match, when the child did recognise a similar odor or a common use product which contains the odor, for example chewing-gum instead of mint, 3 = misrecognition if a completely different odor was recognised or odorant was smell but unidentified, and 4 = negative or failure olfactory experience when no odor was detected at all.

Statistical analyses: continuous variables were presented as mean and 95% CI or median and interquartile range, while categorical variables were described using sample counts and percentages. Continuous variables were compared using an independent *t*-test when we can assume normal distribution or the Mann-Whitney test when normality cannot be assumed. Categorical variables were compared using the chi-square test or Fisher's exact test. All statistical analyses were performed using SPSS version 19.0 and p-value <0.05 was considered statistically significant.

3. Results

A total of 126 paediatric patients (0–15 years old) were screened for COVID-19 infection during the study period (61% were males). No sex differences among groups were found. 69 of them were older than six years and thus candidates to perform the olfactory test.

Among the 33 cases who tested positive for SARS-CoV-2 infection, 22 had both a positive RT-PCR test and anti-SARS CoV-2 ELISA IgG positive titles. The other 11 showed a significant title of anti-SARS CoV-2 IgG in the presence of a negative RT-PCR test. Median time to RT-PCR testing after the onset of symptoms was 8 days (IQR 3,8–23). Serological test was performed at a median time of 51 days (IQR 32–61) after the onset of disease. All the 33 patients showed a clinical context of COVID-19 infection and/or were asymptomatic but had been in close contact with an infected person (12%). Mean age of infected children was 8·4 years (95%CI 6.8–10.1) higher than controls ($p = 0.035$) and ranged between 2 and 15 years.

Results from the questionnaire of olfactory dysfunction clinical symptoms: One patient in the not infected children group (n = 93) referred chronic olfactory disfunction due to an underlying medical condition (cystic fibrosis) and was excluded from the study. Three other children (all female) in the control group refer anosmia during the days of disease and two of them referred also dysgeusia. None of them referred nasal discharge during the process. Two of them performed the odor test (the other one was too young). One of them could recognise 5/7 odorants (except anise and vinegar) and smell all odorants, the other one did not smell vinegar and two other odorants (cinnamon and lemon) were not rightly identified.

Among the infected children, 5/33 (15%) referred having suffered clinical signs of anosmia after the onset of infection. Dysgeusia was present in 4 of them. None of them referred anosmia nor dysgeusia as the first clinical manifestation of disease. No sudden onset symptoms were declared by any of them. Clinical characteristics of these patients are shown on Table 1.

We compared all the clinical symptoms reported by patients to identify differences between the case and control groups. Cephalea ($p = 0.009$) and anosmia ($p = 0.029$) were significantly more frequent in the case group. No differences in length of olfactory symptoms, if they were present, were found between the two groups.

Results from the odor identification test: The odor test was performed in 69 patients, including 20 infected with SARS-CoV-2. As mentioned above, a patient with chronic condition was tested but excluded from all further analyses. Sex distribution was homogeneous between infected children and controls. Mean age was 11.6 years (95% CI 10.5–12.7) for the case-group and 9.5 (95% CI 8.7–10.2) for the controls ($p = 0.002$). Table 2 shows the percentage of recognition/misidentification and failure for every odorant in both groups. The case group showed lower percentages of recognition (misidentification and/or failure to identify odor) for every odorant tested, except for cinnamon. Nevertheless, no statistically significant differences were found.

Median odorant recognition was 3 odors (IQR 2–4) in the case group and 4 (IQR 3–5) in controls ($p = 0.10$). Mint (73%), jasmine (59.4%) and cinnamon (50.7%) were the best recognised odors, both in the whole cohort and in every group when analysed separately. Using their own jargon, children commonly identified jasmine as "perfume" or "flowers", mint was identified as "chewing gum" or "toothpaste", cinnamon as "rice pudding" or "cookies", anise as "rosquillas" (a traditional type of anise-flavored Spanish doughnut), and vinegar was identified as "salad". All patients with self-referred disfunction on the questionnaire did

Table 1
Olfactory disfunction (self-reported questionnaire) among infected children (case group n = 33) and odor test results in these patients.

Patient data	Anosmia length	Dysgeusia length	Other symptoms[a]	Odor test results[b]
Patient 32 Female, 14 y PCR and IgG+	5 days	1 day	Fever, dyspnea (pneumonia), asthenia.	*1 parfum, 2 flower, 3 jasmine, 4 cinnamon, 5 vinegar, 6 cinnamon, 7 lemon*
Patient 104 Male, 12 y PCR and IgG+	15 days	no	Fever, nasal discharge, dyspnea, asthenia, diarrea	*1 not identified, 2 neutral,* 3 mint, *4 plastic, 5 sauce, 6 cinnamon, 7 parfum*
Patient 109 Male, 13 y PCR and IgG+	10 days	no	Fever, cephalea, cough, throat pain, dyspnea, diarrhea	*1 flower, 2 incense,* 3 mint, *4 rise pudding, 5 mayonnaise, 6 soap, 7 not identified*
Patient120 Male 11 y PCR and IgG+	10 days	10 days	Fever, cough, headache, myalgias, skin lesions	*1 not identified, 2 neutral, 3 tooth paste, 4 no odor detected, 5 cinnamon, 6 no odor detected, 7 no odor detected*
Patient 121 Female, 14 y PCR - Ig G + *Sibling of patient 120*	10 days	10 days	Cough, fever, throat pain, cephalea, asthenia, diarrhea	*1 perfum, 2 neutral, 3 tooth paste, 4 anise, 5 cinnamon, 6 no recognition, 7 cinnamon*

[a] First symptom is underlined.
[b] Match results in the odor test are underlined.

recognise a range from 2 to 4 odorants in the test. One of those patients remains anosmic for 3 odors (Table 1). In our sample, there were five asymptomatic but infected children who referred to be normosmic at any time. Only two of them were older than six and performed the test. One identified 6/7 odorants but the other one failed to recognise any of them and was unable to smell 3/7.

Differences in the test results between groups stratified by sex and age were also analysed. In the whole set of tested patients, regardless of infection, female patients identified a median of 4 odors (IQR 3–5), while male patients recognised 3 (IQR 2–4) (p = 0.03). The same significant trend was observed when the analysis was restricted to infected patients. In the full cohort, the jasmine and vinegar odorants were significantly better recognised by females (p = 0.016 and p = 0.049 respectively). Jasmine was recognised by 79.2% of females but only by 50% of males. As mentioned, females also performed better at recognizing a large majority of odors (neutral, mint, cinnamon and lemon), with the only exception of anise, which was better recognised by male patients. In the case group, the lemon odor was only identified by 15% of the patients. All of these were female patients, which revealed a significant difference based on sex (p = 0.031). Infected boys showed higher percentages of recognition of neutral and mint odors when compared to females within the case group, but differences were not significant. In the control group, females performed better at identifying mint (p = 0.009). In this group, as in the whole tested population, all odors except anise were better recognised by females. No significant age differences were found in the pattern of recognition of any of the odors analysed, except for jasmine recognition in the case group. Infected children who recognised jasmine, exactly or closely, were older than those who did not recognise it, with an average age of 12.8 years (CI 11.3–14.2) vs. an average 10.·1 years for those who failed to recognise it (CI 8.8–11.5) (p =0.003). In the control group, no significant age differences were found.

4. Discussion

Subtle disturbances in olfactory patterns after COVID-19 infection have been found in our study in children, especially in males and older ones. Rather than established and/or persistent anosmia, as described in adult patients [1,2,11], children more frequently exhibited failure to recognise odors (misidentification) after infection. Even after correcting for the fact that infected children were older than controls, and so a greater development of the odor learning process should be assumed, our results show higher overall identification percentages for every odorant in healthy children when compared to infected ones. Moreover, healthy children recognised a larger average number of odorants in the test.

Despite the higher frequency of occurrence observed in the results from the odor identification test, past symptoms of anosmia or dysgeusia by the time of illness had only been reported by 5/33 of the infected patients (15%), all of them above eleven years old. In any of these cases, by contrast to what has been described in young adults, anosmia and/or dysgeusia had been referred as the first or only symptom of infection [3]. Some adult series report that anosmia was present in as much as 73% of cases prior to laboratory diagnosis of COVID-19 and was the presenting symptom in 26.6% of all cases [12]. Anosmia had not been even reported by any of the children interviewed as a sudden onset, like feeling a pain in the nose, as has been described in adults [11–13]. Length of disturbances were shorter than described in adults [6] and lasted less

Table 2
Odor identification test results for both groups.

Odorant	Case-group *Sars-Cov-2 Infection* n = 20 patients			Control-group Not infected patients n = 48 patients[b]			p-value[a]
	Identifies (match)	Smell but misidentify	Failure to smell	Identifies (match)	Smell but misidentify	Failure to smell	
Jazmine (A)	11 (55%)	8 (40%)	1 (5%)	30 (62·5%)	18 (37·5%)	–	0·596
Neutral (B)	16 (80%)	4 (20%)	–	43 (89·6%)	5 (10·4%)	–	0·432
Mint (C)	13 (65%)	6 (30%)	1 (5%)	38 (79·2%)	10 (20·8%)	–	0·235
Anise (D)	4 (20%)	15 (75%)	1 (5%)	16 (33·3%)	32 (66·7%)	–	0·272
Vinegar (E)	5 (25%)	13 (65%)	2 (10%)	16 (33.3%)	29 (60·4%)	3 (6·3%)	0·498
Cinnamon (F)	11 (55%)	8 (40%)	1 (5%)	24 (51·5%)	23 (47·9%)	1 (2·1%)	0·707
Lemon (G)	3 (15%)	14 (70%)	3 (15%)	18 (37·5%)	22 (45·8%)	8 (16·7%)	0·067

[a] p value was calculated by comparation of match identification and misidentify and failure.
[b] One patient with chronic olfactory disfunction (Cystic Fibrosis) was excluded for the statistical analysis of data.

than two weeks as it has been published in an adolescent case in Italy who also associated a late-onset skin rash [7].

Meta-analysis of the data from Tong et al. [2] showed a prevalence of olfactory disfunction in infected adults of 52.7% (95% CI, 29.6%–75.2%). Another study based on RT-PCR identification of patients in our country showed a prevalence of self-referred anosmia of 39.2% [13]. Lower prevalence in children compared to adults can be explained by receptor immaturity [14]. The SARS-CoV-2 host cell surface receptor, angiotensin-converting enzyme 2 (ACE2), is highly expressed in nasal mucosa, in particular in the ciliated epithelium and goblet cells. A mouse model has determined that ACE2 and protease TMPRSS2, which further facilitates virus uptake, are expressed mainly in sustentacular cells of the olfactory epithelium and less in other olfactory receptor neurons. Data suggest that sustentacular cells are involved in virus entry and that expression of the entry proteins increases in animals with age [14]. These pathogenic mechanisms could be related to the lower prevalence of olfactory disfunction in children, especially under ten.

Results from surveys of clinical symptoms should be interpreted with caution as self-reporting may have limited value and may be inconsistent in children. One nine-year-old boy referred no symptoms but failed to recognise any of the odorants in the test. The possible recall bias for surveys may also play a relevant role. On the contrary, a more objective approach based on actual controlled measurements, like the test that we performed, may show usefulness in the evaluation of olfactory disfunction in patients of paediatric age. This test has shown its ability to identify subtle differences between groups and quite a good performance for children. Most smells were recognised in an exact or approximate form. Accounting for the fact that infantile discrimination and reporting of one exact odor is difficult, when we performed our analysis children were allowed to refer to the approximate odor translated into infantile jargon that was connected with common life situations like “toothpaste” (for to mint) or “perfume” (for jasmine). Healthy children in the study demonstrated that they can identify nearby 60% of the odorants in the test. It is assumed that a success rate of 70% in odor identification or even less when applied to a multicultural population, is suitable to estimate the usefulness of an odor test in children [15,16].

Analysis of olfactory and gustatory function in children is a neglected area of research across the world and suitable clinical tests for the youngest children need to be improved [17–19]. There is a lack of standardization of the quantitative instruments used to assess children’s sense of smell. There is also great variability in the methodology of the tests, mainly based on identification or discrimination tasks, which reduces the reproducibility and reliability of the results [17]. Some tests such as the 40-odorant UPSIT Smell Identification Test and the Sniffin Sticks Test are available commercially for testing olfaction in adults [20,21] and have been applied to COVID-19 adult patients [8,9]. Although they may be too lengthy for inpatient paediatric patients and contain odorants not well known to be used with young children, some experience with adaptation of the test and application to children has been published, but none in COVID-19 children [22–24].

As we have mentioned above, olfactory tests in children are often based on identification of the odorants. Some of them are supported by photographs, written options or other tools with the intention to help the child in its performance [25,26]. This test is based exclusively in the olfactory recognition and then on olfactory memory of children. Odorants were blindfolded and no feedback was given during the task. Due to the lack of odor knowledge, children may perform poorly on identification tests like ours. Also, their olfactory memory is underdeveloped [27,28]. We established the lower age limit of six years to perform the test because odor measurement may be often unreliable below this age [16]. We found no differences on the average age of those who recognised every single odorant compared to those who did not, except for flower odorant recognition in older children in the infected group. This supports the usefulness of this test even in younger patients. In the general population, flower recognition has been shown to be worse in young children, particularly in those under six years [17]. Girls outperformed boys, as previously described, a fact that some authors connect with their better linguistic performance [16,21–24]. To achieve better results in this kind of tests it is suitable to employ friendly odors according to cultural context. In our study, the odorant best recognised was mint, followed by jasmine. Cinnamon was recognised by half of the patients although previous studies have described that cinnamon was an odorant poorly identified in children, with identification reaching almost chance level [16]. For some children it has been described as unpleasant. Odor pleasantness has been related to odor familiarity and positively associated with correct odor identification in children [29]. Parosmia has been described linked to COVID infection in adult patients, especially in later stages of the disease when osmic recovery begins [3]. Vinegar, lemon and anise were more poorly recognised by children. Lemon is extremely volatile and thus the odorant may have easily vanished. Olfactory-trigeminal stimulus (vinegar) was identified by a reduced number of children and/or described as unpleasant odor; in some children with COVID 19 infection, vinegar was misidentified for cinnamon, these findings will require follow-up studies to further determine their significance.

In summary, we propose a novel test that offers great advantages it terms of simplicity, as no trained personal is needed to administer it. The fact of being individually packaged, using single-use smell strips also make it clean and compliant with basic safety considerations that are critical in the middle of a pandemic. Our test could be employed in osmic rehabilitation processes and for early diagnosis in children diseases linked to olfactory disfunction like autism [30]. Broader studies are needed to confirm and improve description of olfactory alterations in paediatric COVID-19 patients.

Contributors

ACG, RNC, MLGD, MPR and IGG contributed to the literature search. ACG and IGG contributed to study design. ACG, AFO and IFP contributed to data collection. ACG, IGG and CMR contributed to data analysis. ACG, RNC, MLGD, MPR and IGG contributed to data interpretation. ACG, CMR and IGG contributed to writing of the manuscript.

Data sharing

Requests for data should be made to the corresponding author.

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Declaration of competing interest

All authors declare no competing interests.

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