MAIN TEXT:

i. A statement with potential conflict of interests related to the manuscript content.

Conflict of interest: all authors declare no conflict on interests related to this manuscript.

ii. Financial support.

Financial support: none

iii. Abstract and keywords.

No abstract provided.

Keywords: COVID-19, olfactory dysfunction, gustatory dysfunction, anosmia, ageusia, children, paediatric population.

iv. Main text.

To the Editor:

Olfactory and gustatory dysfunctions (OGD) have been reported as relevant symptoms that may predict presence of coronavirus disease 2019 (COVID-19) in adults, associated with mild or moderate disease[1, 2, 3]. However, published data on OGD in children are scant, likely due to several factors specific to the pediatric population such as a lower incidence of infection, the tendency of COVID-19 to be asymptomatic[4, 5], and the difficulty of studying childhood OGD with objective methods. Two case reports have been published to date: one with 3 adolescents[6], and the other describing a 17-year-old girl with beta-thalassemia who presented total loss of smell and taste for 8 days[7]. Current data on the prevalence of OGD are based on only 2 small cohorts of COVID-19–positive children[8, 9]. In a related study, Mannheim et al.[10] describe that 19 (30%) of 64 infected children (0–17 years old) presented nasal congestion, rhinorrhea, and total loss of smell, though providing no data on the exact number of patients with olfactory dysfunction exclusively.

The present study aimed to evaluate OGD among symptomatic COVID-19 children presenting to a referral pediatric hospital for this disease in Madrid, Spain. The database of positive SARS-CoV-2–RT-PCR (reverse transcription-polymerase chain reaction) cases diagnosed between March 20 and July 13, 2020 was retrospectively reviewed. Demographic information, COVID-19 symptoms, disease severity and clinical course, comorbidities, and blood biomarkers were obtained from electronic medical records. Information on smell and taste disorders and any incomplete data on other COVID-19 symptoms was obtained by telephone interview with parents and patients, who provided oral consent. COVID-19 severity was established according to the classification by Qiu[9]. Questionnaire data on onset, duration of smell and taste disorders was used, and severity was classified according to a scale modified from Izquierdo-Dominguez et al. [1] Based on

the degree of smell or taste loss, we stratified patients as normosmic-mild (0–3 points), moderate (4–6 points), or severe loss (7–10 points).

Qualitative variables are expressed as numbers and percentages, and the Chi-square test was used for comparison. Quantitative variables appear as mean and standard deviation or median and interquartile range (IQR) according to their distribution. Normality of age distribution was confirmed by the Shapiro-Wilk test. ANOVA test and the DMS as post hoc test were used to compare normally distributed variables. Statistical significance was set at 95% ($p < 0.05$).

Ninety-two children were identified as SARS-CoV-2–RT-PCR positive; 2 declined to participate. Asymptomatic patients were excluded. Fifty patients were diagnosed with symptomatic COVID-19 (52% male; mean age: 7±7 years, IQR: 6 months–12 years). Patients under 6 years of age (n=20) were excluded for potential poor reliability on self-reported smell function. Thirty patients were finally enrolled (Figure 1). Seven (23.3%) patients presented mild COVID-19, 11 (36%) were moderate cases, and 12 (40%) had severe disease. Nineteen (63.33%) required hospitalization, and 11(36.6%) were discharged after emergency department evaluation.

A total of 8 (26.6%) (range 9–17 years of age) of 30 symptomatic children presented OGD; they were older than the children without OGD (12.6 ± 2.7 years vs. 10.6 ± 3.1 years, respectively; p=0.045). Five (16.6%) of 30 COVID-19–positive children presented both smell and taste disorders and 3 (10%) had gustatory dysfunction only (Figure 1). OGD was severe in all patients (7–10 points) (Tables 1 and 2).

OGD onset was sudden in all patients; 6 developed symptoms simultaneously with the other COVID-19 symptoms, and 2 (25%) before other disease manifestations. Of the latter, one developed both symptoms, and the other only gustatory dysfunction (Table 2). In no case did OGD appear as the only symptom. OGD was transient in all patients, [median olfactory dysfunction duration, 45 days (range 15–120 days), and median gustatory dysfunction of 10 days (5–120 days)] (Table 1).

There was no significant difference in the prevalence of OGD with respect to the severity of COVID-19 (mild 4.3%, moderate 36.4%, severe 25%) nor in COVID-19 severity between patients with and without OGD (Table 1) (p=0.578). Five patients with OGD (62.5%) were hospitalized (2 in the intensive care unit). Seven subjects presented digestive symptoms, 6 had fever (>37.8ºC), 4 cutaneous manifestations, 3 pneumonia, 2 odynophagia, and 1 dyspnea. All patients recovered without sequelae except for one asthmatic patient with exercise-induced dyspnea (case 4) (Table 2). Inflammatory markers are described in Table 1.

The prevalence of OGD in this cohort was 26.6%, a much lower rate than that reported in adults[1, 2, 3], including the European multicenter study by Lechien et al.[3] in which 85.6% and 88.0% of COVID-19 patients reported olfactory and gustatory dysfunctions, respectively, as well as a Spanish study in which 53.7% and 52.2% of patients presented severe smell or taste loss, respectively[1]. Furthermore, the

prevalence of OGD in our study is somewhat lower than in the multicenter Qui et al. study[9], which included 27 children (6–17 years old), with 10 of 27 (37%) subjects (15–17 years of age) presenting OGD. In contrast, Erdede et al.[8] detected a lower prevalence (3.7%) than ours, reporting only 1 child with taste loss among 27 COVID-19–positive children.

In our study, 10% of patients had isolated gustatory dysfunction, an uncommon but previously reported feature in adults[3] and children[8]. The degree of OGD has not been previously described in the pediatric population, and according to our findings, all subjects experienced a severe symptomatic form.

Our patients with OGD were somewhat younger than in the study by Qui et al.[9] (12.6 ± 2.7 years vs. 16.6 ± 0.7, respectively); in our population, however, children who developed OGD were older than those who did not. This could be explained by a lesser susceptibility to OGD among younger children or lower diagnostic accuracy. Our patients seemed to have more severe COVID-19 than in other reports in pediatric[9] and adult subjects[1, 3]. However, the severity in patients with OGD was not significantly different than OGD-free individuals, nor among patients with OGD, although our limited sample size is a potential source of bias.

As described by Qiu et al.[10], OGD onset coincided with other symptoms in most patients, thus preventing its use as an early sign of COVID-19 in children. The duration of OGD was between 5 and 120 days, which is longer than that reported by Mak et al.[6] (3->13 days), possibly due to a longer follow-up in our study. Interestingly, loss of smell resolved before loss of taste in our cohort.

The limitations of this study include the potential bias from selecting a population treated in a tertiary hospital, which may not reflect the entire spectrum of COVID-19 in children, particularly mild forms. Further limitations are the retrospective study design and the lack of an objective, validated method to assess OGD.

In summary, this is one of the few reports in Europe describing OGD in children with COVID-19. In the pediatric population with predominantly moderate to severe COVID-19 presented here, OGD displayed a low prevalence, was not an early sign of disease onset, and tended toward a severe and long-lasting course.

v. Acknowledgments.

None.

vii. References.

1. Izquierdo-Domínguez A, Rojas-Lechuga MJ, Chiesa-Estomba C, Calvo-Henríquez C, Ninchritz-Becerra E, Soriano-Reixach M, et al. Smell and taste dysfunctions in COVID-19 are associated with younger age in ambulatory settings-a multicenter cross-sectional study. J Investig Allergol Clin Immunol. 2020; 30(5): 1-28.

2. Kaye R, Chand CWD, Kazahaya K, Brerton J, Denneny JC 3rd. COVID-19 Anosmia Reporting Tool: Initial Findings. Otolaryngol Head Neck Surg. 2020; 163(1): 132-134.

3. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020; 277(8): 2251-2261.

4. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among Children in China. Pediatrics. 2020; 145 (6): e20200702.

5. Han MS, Choi EH, Chang SH, et al. Clinical characteristics and viral RNA detection in children with coronavirus disease 2019 in the Republic of Korea. JAMA Pediatr. 2020; 00: e1-e8.

6. Mak PQ, Chung KS, Wong JS, Shek CC, Kwan MY. Anosmia and ageusia: not an uncommon presentation of covid-19 infection in children and adolescents. Pediatr Infect Dis J. 2020; 39(8): e199-e200.

7. Marhaeni W, Wijaya AB, Kusumaningtyas P, Mapianto RS. Thalassemic Child Presenting with Anosmia due to COVID-19. Indian J Pediatr 2020; 87(9): 750.

8. Erdede O, Sarı E, Uygur Külcü N, Yalçın EU, Sezer Yamanel RG. An overview of smell and taste problems in paediatric COVID-19 patients. Acta Paediatr. 2020; 00: 1-3.

9. Qiu C, Cui C, Hautefort C, Haehner A, Zhao J, Yao Qi et al. Olfactory and Gustatory Dysfunction as an Early Identifier of COVID-19 in Adults and Children: An international Multicenter Study. Otolaryngology-Head and Neck Surgery. 2020; 00: 1-8

10. Mannheim J, Gretsch S, Layden JE, Fricchione MJ. Characteristics of Hospitalized Pediatric COVID-19 Cases - Chicago, Illinois, March - April 2020. J Pediatric Infect Dis Soc 2020; 00: 1-14.

viii. Tables (each table complete with title and footnotes).

TABLE 1: Characteristics of COVID-19 symptomatic children presenting with olfactory and/or gustatory dysfunction (OGD).

IQR: interquartile range; SD standard deviation, PICU: paediatric intensive care unit

* p=0.045

† From reference 9. Qiu C, et al. Qiu classification for COVID-19 grade of severity: mild (low fever, mild cough, slight fatigue, and no evidence of pneumonia on imaging), moderate (fever and respiratory symptoms, and evidence of pneumonia on imaging), severe (dyspnea, tachypnea, desaturation or radiologic worsening

over 24–48 hours) and critical (respiratory failure, septic shock, and/or multiple-organ dysfunction).
‡: Modified from reference 1. Izquierdo-Domínguez A, et al. Normosmic-mild (0–3 points), moderate (4–6 points), and severe olfactory or gustatory loss (7–10 points).

TABLE 2: Description of patients with COVID-19 and olfactory and /or gustatory dysfunction.
OGD: Olfactory and gustatory dysfunction; GD: Gustatory dysfunction; OD: Olfactory dysfunction; N/A: Non applicable; NA: Not available; PICU, Paediatric intensive care unit.
† Modified from reference 1. Izquierdo-Domínguez A, et al.
‡ From reference 9. Qiu C, et al.

ix. Figure legends.
FIGURE 1: Flowchart of the study.
† Exclusion criteria previously established.
‡ RT-PCR reverse transcription-polymerase chain reaction

x. Appendices (if relevant).

None.