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Characteristics Associated with Olfactory and Taste Disorders in COVID-19

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COVID-19 · Severe acute respiratory syndrome coronavirus-2 · Anosmia · Ageusia · Headache

Abstract
Introduction: Olfactory and taste disorders (OTDs) have been reported in COVID-19 caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the mechanisms of which remain unclear. We conducted a detailed analysis of OTDs as part of 2 seroepidemiological investigations of COVID-19 outbreaks. ***Methods:*** Two retrospective cohort studies were conducted in a high school and primary schools of Northern France following a COVID-19 epidemic in February-March 2020. Students, their relatives, and school staff were included. Anti-SARS-CoV-2 antibodies were identified using a flow-cytometry-based assay detecting anti-S IgG. ***Results:*** Among 2,004 participants (median [IQR] age: 31 [11–43] years), 303 (15.2%) tested positive for SARS-CoV-2 antibodies. OTDs were present in 91 (30.0%) and 92 (30.3%) of them, respectively, and had 85.1 and 78.0% positive predictive values for SARS-CoV-2 infection, respectively. In seropositive participants, OTDs were independently associated with an age above 18 years, female gender, fatigue, and headache. ***Conclusion:*** This study confirms the higher frequency of OTDs in females than males and adults than children. Their high predictive value for the diagnosis of COVID-19 suggests that they should be systematically searched for in patients with respiratory symptoms, fever, or headache. The association of OTDs with headache, not previously reported, suggests that they share a common mechanism, which deserves further investigation.

Introduction

Olfactory and taste disorders (OTDs) have been reported to be strongly associated with the diagnosis of COVID-19 in patients with flu-like illness [1]. They are often

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associated and can occur in patients without nasal obstruction [2]. A prevalence of 52.7% for olfactory and 43.9% for taste disorders in patients with COVID-19 [3], together with a 61% positive predictive value (PPV) for the diagnosis of COVID-19 for olfactory disorders [4], have made OTDs particularly relevant for the diagnosis of COVID-19 since the beginning of the pandemic. Data on long-term outcome are still scarce but reports suggest significant proportions of incomplete recoveries [5, 6]. Yet, mechanisms underlying OTDs remain poorly elucidated. To provide a better understanding and suggest hypotheses on the origin of OTDs observed in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, we conducted a detailed analysis of OTDs as part of 2 seroepidemiological investigations of COVID-19 outbreaks.

Methods

We conducted 2 retrospective cohort studies following the recent COVID-19 epidemic in a city in Northern France that was one of the first localities hit by the COVID-19 outbreak in February 2020. Details of the study methods and recruitment have been described elsewhere [7]. In short, pupils from the town's high and primary schools as well as teaching and nonteaching staff were invited to participate. Since most pupils were minor, at least 1 parent was invited to participate in the study, to provide informed consent for their child and for any of the other children over the age of 5 years in the household invited to participate. Following informed consent, participants completed a questionnaire which covered sociodemographic information, underlying medical conditions, history of symptoms since January 13, 2020, including OTDs and history of COVID-19 diagnosis prior to this investigation. Symptoms were considered only if they occurred at least 7 days prior to the date of blood sample collection to allow time for seroconversion. Investigated symptoms included fever defined as body temperature above 38°C, cough, dyspnea, olfactory impairment, taste impairment, muscle ache, throat ache, rhinitis, diarrhea, headache, fatigue, along with their respective dates of onset and resolution. Data about past medical assistance including hospitalization for reported symptoms were also collected. We considered report of past olfactory or taste disorders unreliable under the age of 15.

A 5 mL blood sample was taken from all participants. We identified anti-SARS-CoV-2 antibodies using an S-flow assay, a flow-cytometry-based assay detecting anti-S IgG, which was developed by Institut Pasteur. We chose cutoffs to attain a specificity >99% based on a previous evaluation performed on sera from 240 pre-epidemic blood donors [8]. In a further study using the same cut-off, the S-Flow assay was shown to have a sensitivity of 99.4% to detect mild forms of RT-PCR confirmed COVID-19 [9].

Factors associated with the presence of OTDs among seropositive participants were identified through multivariable logistic regression analysis. Variables introduced into the model were sociodemographic and clinical variables. Variables were removed through backward selection until all variables had p value <0.05 (with a tolerance up to 0.07, i.e., marginally significant, for variables of clinical relevance). All statistical analyses were performed using Stata 15.0 (StataCorp, College Station, TX, USA). An independent Ethics Committee (Comité de Protection des Personnes) approved the studies on February 19, 2020. We conducted the studies from March 30 to April 4, 2020, in the high school, and from April 28 to 30, 2020, in the primary schools. They are registered with ClinicalTrials.gov (NCT04325646).

Results

From March 30 to April 4, 2020, 878 of 1,262 high school pupils, teachers, and nonteaching staff were invited by email to participate in the investigation (email addresses were not available for 384). Of these, 323 (36.8%) responded. An additional 348 parents and siblings of the 243 high school pupils joined the study. Blood samples could not be obtained from 7, making a total of 664 study participants.

From April 28 to 30, 2020, 1,047 pupils and 51 teachers from 6 primary schools were invited by email to participate in the investigation. Of these, 541 (51.5%) pupils and 46 (90.2%) teachers accepted to participate in the study. Thirty-one pupils were excluded as they refused phlebotomy, as were 4 teachers not directly affiliated with any of the 6 schools. This resulted in 510 pupils and 42 teachers with a blood sample to be analyzed. In addition, 641 parents of pupils, 119 relatives of pupils sharing the same household, and 28 nonteaching staff completed the study population. This formed a population of 2,004 participants, 664 in the first study conducted in the high school and 1,340 in the second study in the 6 primary schools, including 749 pupils (37.4%), 151 teaching and nonteaching staff members (7.5%), and 1,104 relatives of pupils (55.1%).

A total of 303 participants (15.2%) were seropositive for SARS-CoV-2. Their median (IQR) age was 31 (11–43), and 140 were under 18 years of age. 135 of them were pupils (44.6%), 42 were staff members (13.9%), and 126 were relatives of pupils (41.6%).

Among seropositive participants, 105 (34.7%) reported OTDs (including 21 participants under 18 years of age): 91 (30.0%) with olfactory disorders, 92 (30.4%) with taste disorders, and 78 (25.7%) presenting with both OTDs. None of the 53 included participants aged 14 years or less reported OTDs.

Proportions of seropositive participants with OTDs and PPVs of these symptoms by gender and age-group are presented in Table 1. Considering only seropositive participants above 14 years of age, characteristics independently associated with olfactory disorders were age

Table 1. Proportion of OTDs among participants who were seropositive to SARS-CoV-2 and PPV for the diagnosis of SARS-CoV-2 infection

Gender	Age, year	Olfactory disorders		Taste disorders	
		Proportion with symptom	PPV	Proportion with symptom	PPV
Male	<18	3/54 (6%)	3/7 (43%)	3/54 (6%)	3/7 (43%)
	≥18	16/52 (31%)	16/18 (89%)	17/52 (33%)	17/22 (77%)
Female	<18	13/85 (15%)	13/15 (87%)	14/85 (16%)	14/17 (82%)
	≥18	59/112 (53%)	59/67 (88%)	58/112 (52%)	58/72 (81%)
Overall		91/303 (30%)	91/107 (85%)	92/303 (30%)	92/118 (78%)

OTD, olfactory and taste disorder; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; PPV, positive predictive value.

between 18 and 44 years (OR = 3.68, 95% confidence interval [CI] = 1.81–7.44) and above 45 years (OR = 2.00, 95% CI = 0.90–4.41) compared to 15–17 years, female gender (OR = 2.34, 95% CI = 1.24–4.41), fatigue (OR = 1.96, 95% CI = 1.03–3.73), and, with borderline statistical significance, headache (OR = 1.83, 95% CI = 0.97–3.43) (Fig. 1). Characteristics independently associated with taste disorders were age between 18 and 44 years (OR = 3.32, 95% CI = 1.65–6.67) and above 45 years (OR = 1.77, 95% CI = 0.81–3.89) compared to 15–17 years, female gender (OR = 2.17, 95% CI = 1.16–4.07), fatigue (OR = 2.27, 95% CI = 1.20–4.30), and, with borderline statistical significance, headache (OR = 1.81, 95% CI = 0.96–3.38) (Fig. 1). Among the 57 participants with both headache and taste disorders as well as for the 57 participants with both headache and olfactory disorders, 41 (72%) reported taste or olfactory disorder onset within 3 days following headache onset.

Discussion

The overall prevalence of OTDs among participants with SARS-CoV-2 infection varied by age and gender being more common among females than males and adults than children. The higher frequency among females has been reported elsewhere [2] and remains unexplained. No child aged 14 or younger reported OTDs. This may partly be due to difficulties for children to identify and report this type of symptoms. However, the lower frequency of OTDs among 15–17 years than adults suggests that underreporting is not the only explanation. Interestingly, 2 other studies about OTDs in SARS-CoV-2 infection found a decreased prevalence of OTDs in elderly patients [10, 11]. These studies included more severe and older patients than our study population. Altogether, these findings suggest a higher frequency among people aged 18–44 years than adolescents and older individuals.

OTDs had higher PPVs for the diagnosis of COVID-19 than previously documented [4], confirming their value for identifying patients with COVID-19. In multivariable analysis, OTDs were independently associated with headache and fatigue among participants with SARS-CoV-2 infection. Onset of OTDs and headache were concomitant in most patients. The association of OTDs and headache, not reported before, may suggest a common mechanism triggering those symptoms. Butowt and von Bartheld [12] detail the possible explanations for OTDs in COVID-19: through nasal obstruction, damage or death of olfactory neurons, alteration of sustentacular cells adjacent to olfactory neurons, or direct alteration of olfactory brain centers by SARS-CoV-2. The absence of nasal congestion of many participants reporting olfactory disorders speaks against nasal obstruction as an explanation. Recent case reports in patients displaying COVID-19-related anosmia without any other neurological symptoms have shown magnetic resonance imaging signs of central nervous system involvement including olfactory bulbs edema and posterior gyrus rectus (a cortical region associated with olfaction) FLAIR hyperintensity [13, 14], as well as PET-CT images of hypometabolism of the left orbitofrontal cortex [15]. An autopsy series has found presence of SARS-CoV-2 via qRT-PCR in the olfactory bulbs of 3 deceased patients and in olfactory neurons, in favor of neuroinvasion through neural-mucosal interface

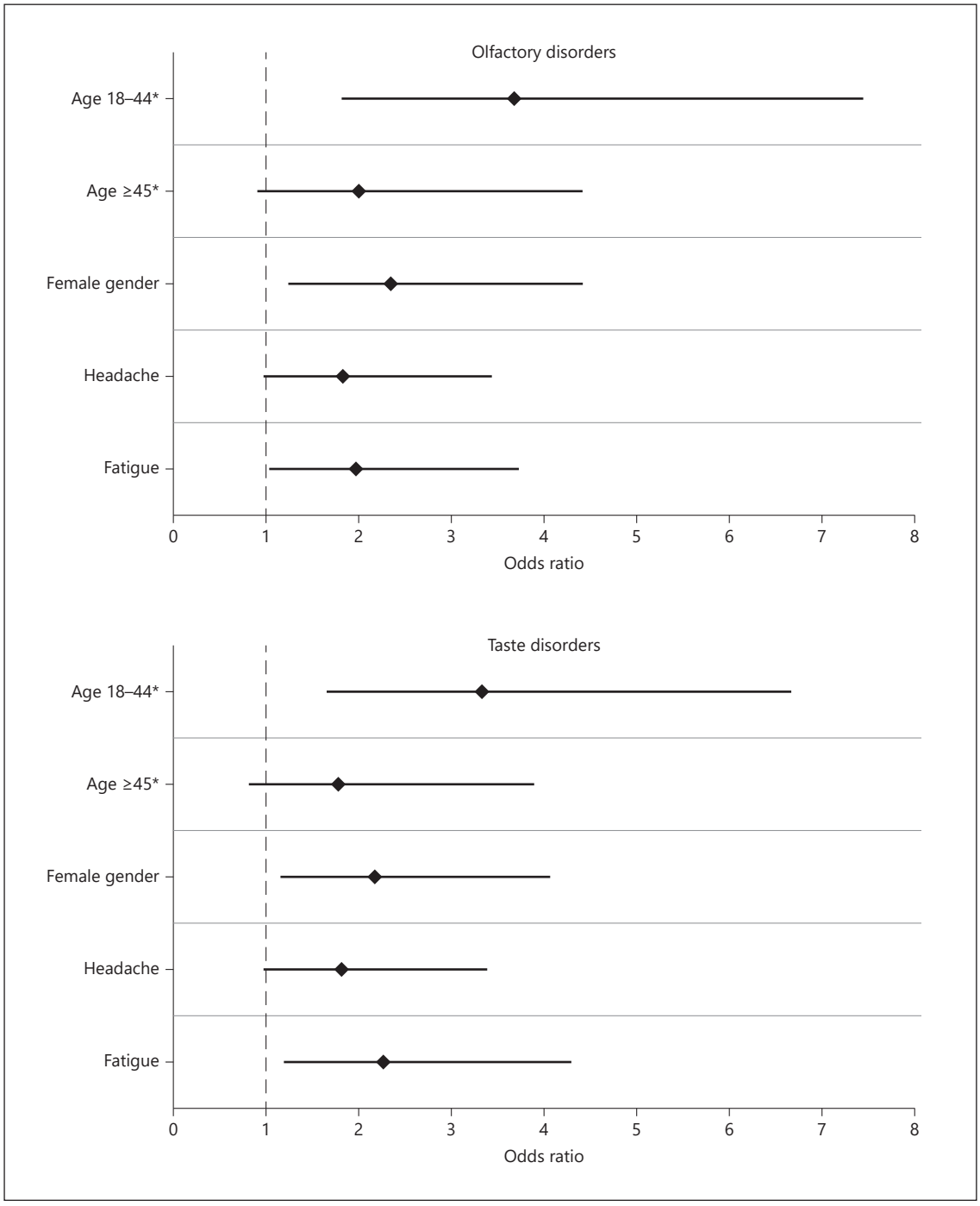

Fig. 1. Characteristics associated with olfactory and taste disorders in SARS-CoV-2 seropositive participants.

up to the olfactory tract of the central nervous system [16]. These findings suggest a direct central nervous system involvement by SARS-CoV-2 in patients with anosmia, which may also explain headache. Cerebrospinal fluid analysis with search for SARS-CoV-2 during symptoms could help verify the hypothesis of a transient central nervous system involvement, although isolated transient OTDs are not an indication for a lumbar puncture.

Alternatively, loss of smell could be caused by the altered function of olfactory neuroepithelium through the infection of the supporting cells and vascular pericytes of the olfactory epithelium [17], findings supported by a recent animal study on hamsters showing damage on olfactory epithelium, with infection of sustentacular cells but none in the olfactory bulbs [18]. Data of human nasal specimens show an increased expression of angiotensin-converting enzyme 2 (ACE2), the receptor to which SARS-CoV-2 binds to enter cells, in the olfactory neuroephithelium, mostly on sustentacular cells but without any expression in olfactory neurons [19]. Usual quick and full recovery of OTDs speaks for such a peripheral mechanism of direct olfactory neuroepithelium alteration by SARS-CoV-2 [20]. The origin of ageusia remains largely unexplained. It may be a consequence of smell disorder as both functions are closely related unless the high expression of ACE2 in epithelial cells of the oral mucosa explains epithelial alteration by SARS-CoV-2 responsible for ageusia [21].

A limitation of the study is the relatively low participation rate among all those invited. It is difficult to speculate however how this has affected the study findings, that is, the proportion with OTDs, the predictive values of OTDs, or the factors associated with OTDs. Symptoms, including OTDs, were self-reported. This may have introduced some misclassification in the study outcome. However, although the participants were not aware of their SARS-CoV-2 serological status at the time of symptoms reporting, OTDs had high PPV for COVID-19 diagnosis, suggesting that self-reporting was reasonably accurate. While influenza may cause OTDs, it is not as common as in COVID-19 [22, 23], making unlikely that OTDs in seropositive participants in our study were caused by flu. Further studies will be necessary to determine overall prognosis of OTDs in SARS-CoV-2 infection and potential prognostic factors.

In conclusion, this study confirms the higher frequency of OTDs in females than males and adults than children. Their high predictive value for the diagnosis of COVID-19 suggests that they should systematically be searched for in patients with respiratory symptoms, fever, or headache. The association of OTDs with headache, not previously reported, suggests that they share a common mechanism, which deserves further investigation.

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Statement of Ethics

The authors state that the experiments were undertaken with the understanding and oral consent of each subject (with a written registration of the consent by the investigator) and that the study conforms with the World Medical Association Declaration of Helsinki. An independent Ethics Committee (Comité de Protection des Personnes) approved the studies on February 19, 2020.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.G., I.C., M.-N.U., S.F.R., B.H., O.S., and A.F. designed the investigation. S.G., T.B., I.C., M.-N.U., S.F.P., B.H., and A.F. developed the study questionnaire. Y.M., L.T., I.C., and S.F.P. managed the data collection. S.F.P. and B.H. oversaw the adherence of the study to the regulatory requirements. Y.M. and L.T. oversaw the collection of the data and maintained the database. T.B., L.G., I.S., M.-N.U., C.R., and O.S. oversaw the collection of the biological samples and the performance and interpretation of biological tests. S.G., Y.M., L.T., B.H., and A.F. performed the statistical analyses. S.G., B.H., and A.F. drafted the first versions of the manuscript. All the authors critically reviewed and approved the final version of the manuscript.

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