PERSPECTIVE

The olfactory and gustatory impairment in COVID-19 evolved clinically, virologically, and immunologically

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ABSTRACT

A well-known COVID-19 red signal is new-onset Olfactory and Gustatory Dysfunction (OGD). Despite this, its clinical, virological, and serological characteristics are still up for discussion. In this cohort research, 170 patients with new-onset OGD were recruited in a systematic manner. At baseline and after one (T1), two (T2), and four weeks, otolaryngological examinations, OGD subjective grading, nasopharyngeal swabs (NS) for SARS-CoV-2 RNA detection, and serum samples collection for SARS-CoV-2 IgG quantification were performed (T3). Infection with SARS-CoV-2 was found in 79 percent of the patients. Specifically, SS analysis was used to discover 43% of positive individuals. In 10% of instances, the OGD was the only clinical symptom. 45 percent of patients said they had Sino nasal symptoms at the same time. At T3, 97 percent of patients reported subjective improvement, with 40 percent fully recovering. The only characteristics linked to OGD severity were hormonal abnormalities and RNA detectability in NS. Patients with systemic involvement and severe OGD had a poorer recovery rate after receiving seasonal influenza immunization. Recovery was not linked to RNA levels or IgG titers. Clinical, virological, and serological aspects of COVID-19-related OGD were tracked throughout time, providing useful insights into the link between host traits and chemosensory dysfunctions for future research.

Key Words: *COVID-19; Olfactory and Gustatory Dysfunction (OGD); Immunity*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been declared a pandemic by the World Health Organization (WHO), with about 178 million confirmed cases and over 3 million deaths as of June 2021. Apart from nonspecific presenting symptoms, Olfactory and Gustatory Dysfunction (OGD) quickly emerged as one of the most prominent aspects at beginning, particularly in paucisymptomatic individuals and in the early stages of the disease. OGD and viral infections are often found together, especially in otolaryngology, where OGD is often associated with nasal blockage and discharge. Nonetheless, OGD is only a slightly connected with Sino nasal symptoms in COVID-19 individuals. It also has a quick and early start, and is frequently the sole symptom described. SARS-CoV-2 infection is common in new-onset OGD patients, while the frequency varies greatly between studies (74–94 percent). Despite this, little is known regarding its relationship to epidemiological factors and comorbidities. Furthermore, only a few research looked at the relationship between viral load on the one hand and the characteristics of chemo sensitive dysfunction on the other, without taking into account serological markers. Finally, to our knowledge, neither cross-sectional or prospective investigations using both serology and molecular assays to better identify the frequency of SARS-CoV-2 infection in new-onset OGD have been done to date. The purpose of this study was to use genetic and serological quantitative tests to examine the frequency of SARS-CoV-2 infection in new-onset OGD patients across time. In addition, baseline severity, resolution rate, and timing of OGD were studied, with distinct severity and resolution patterns being linked to significant clinical, virological, and immunological aspects.

The goal of this study was to track the clinical, virological, and immunological characteristics of COVID-19-related OGD across time. Several investigations have shown that the OGD is an effective clinical marker for COVID-19, with a positive predictive value of 61%, despite the fact that its relevant specificity (93–99%) is not matched by a similarly high sensitivity (23–43%). The OGD validated its clinical significance throughout our analysis, since it was the sole complaint recorded in 10.5 percent of positive individuals. Even in cases of systemic illness, chemosensory impairment was found to be critical for diagnosis, as the OGD predicted GSS by 5 days (IQR 2–8) in 10.1 percent of patients. Based on NS and SS studies combined, the total prevalence of SARS-CoV-2 infection was 79 percent. The majority of research looking at the prevalence of SARS-CoV-2 in OGD patients, such as those by Lechien (88%), Salmon-Ceron (94%), and Hopkins (74%), relied on NS findings one. So far, only two studies have used SS testing: a preliminary report from our research group (75%), and a cross-sectional study using only qualitative point-of-care serological kits (77.6 percent). To our knowledge, this is the first study to use both NS and SS to determine SARS-CoV-2 prevalence in a controlled clinical context. Notably, our findings showed the need of serological testing in the identification of COVID-19 in OGD patients. In fact, serological essays were used to detect more than 40% of COVID-19 cases, showing that NS or SS alone may have overestimated SARS-CoV-2 frequency. This might be due to the time between the start of symptoms and test confirmation. Indeed, as we previously reported in a smaller sample, the vast majority of patients produced SARS-CoV-2 IgG three weeks after beginning of symptoms, but RNA detectability in NS declined with time. In terms of clinical aspects, research shows that COVID-19-related OGD typically manifests as a mixed illness, impacting both smell and taste in the majority of patients. Our findings corroborate previous research, with 96 percent of patients reporting both deficits. Despite the notion that retro-nasal olfaction may play a role in flavor perception, new research suggests that direct viral involvement is the major cause of COVID-19 gustatory impairment. Recently, the expression of Angiotensin-Converting Enzyme-2 (ACE-2) — the primary cell receptor for SARS-CoV-2 – was discovered in the taste organs of mice.

Only endocrine problems and RNA detectability in the NS were substantially linked with greater baseline OGD severity. Because the olfactory and endocrine systems are so closely related, metabolic diseases have been shown to have an impact on smell and taste. Crosstalk between the olfactory system and the hypothalamus is enabled through axonal projections to and from the olfactory bulb. Furthermore, the olfactory mucosa and bulb cells express metabolic homeostatic receptors and peptides. Despite the overall trend of improvement, only 40% of patients at T3 had fully recovered from the OGD. The resolution rate appears to be diverse in the literature, ranging from 13% to 86 percent, with the period of follow-up and OGD evaluation approach (quantitative vs qualitative), being the most important factors. In our study, the most important factor determining full resolution was the severity of the beginning. Other research looking at the progression of chemosensory deficits in COVID-19 back this up. To

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our knowledge, the relationship between OGD and GSS has never been thoroughly examined. GSS were linked to a reduced risk of full recovery in our research. It's possible that systemic involvement reflects a more severe SARS-CoV-2 infection and, as a result, decreased body's ability to cope with the virus. In a preliminary assessment on 121 COVID-19 patients, Lovato et al. discovered that among GSS, the absence of fever was substantially linked with persisting OTD. Because severe COVID-19 is linked to fever, the authors hypothesis that individuals with OGD who do not have a temperature will have a mild-moderate COVID-19. However, no definitive conclusions can be reached at this time, and further research is needed to adequately examine this concept. Surprisingly, a link between influenza vaccination and full recovery at T3 was also discovered. Flanagan observed similar results prior to the current epidemic, pointing out that influenza vaccination rates were much lower among OGD patients. Furthermore, intranasal vaccination showed attenuation capabilities on both viral location and olfactory bulb inflammation in mouse models. These findings, together with our findings, provide intriguing leads for future clinical and experimental research targeted at better understanding the link between acquired immunity and chemosensory dysfunctions.

Furthermore, there were no significant differences between patients with and without nasal symptoms in terms of OGD baseline severity, course, or resolution rate. Nasal inflammation and mucosal swelling can prevent olfactory molecules from reaching the olfactory clefts, hence Sino nasal symptoms alone can lead to olfactory dysfunctions. The persistence of olfactory deficits following the acute phase of COVID-19, even in the absence of severe nasal symptoms, supports the concept of direct injury to both the olfactory epithelium and central olfactory pathways. SARS-CoV-2 is a neurotropic virus that can move from the olfactory system to the brain and spinal cord. Several studies have shown viral transmission via the olfactory neuroepithelium to the olfactory bulb. In human specimens, ACE-2 and TMPRSS2, which are necessary for SARS-CoV-2 entrance in host cells, were found in sustentacular and olfactory stem cells. SARS-CoV-2 has been shown to infect the central nervous system, with MRI evidence of olfactory bulb abnormalities in anosmic COVID-19 patients. In the olfactory bulbs of individuals with severe COVID-19, SARS-CoV-2 particles, diffuse infiltration of CD163-positive macrophages, and cytotoxic T cells have also been seen. Furthermore, evidence is accumulating that SARS-CoV-2 plays a role in determining olfactory impairment by inhibiting the fast turnover of olfactory receptors. Recent research suggests that SARS-CoV-2 may assault the nasal serous gland, preventing the synthesis of growth factors required for stem cell activation and transformation in olfactory receptors. Finally, the role of several possible pathogeneses in COVID-19's olfactory impairment warrants additional investigation.

CONCLUSION

The current longitudinal investigation reveals the virological and immunological characteristics of COVID-19-related OGD throughout time. The combination of SS and NS, in particular, appears to be critical in identifying a larger incidence of positive COVID-19 individuals with OGD. In cases with RNA detectability in NS and associated endocrine diseases, the severity of OGD was observed to be greater. Higher intensity at beginning, as well as systemic symptoms, resulted with worse recovery rates. On the other hand, participants who had influenza vaccination had a better recovery rate, pointing to further investigation into the link between acquired immunity and chemosensory dysfunctions.