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COVID-19 and olfactory dysfunction - an ENT perspective to the current COVID-19 pandemic

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ABSTRACT

The current COVID-19 or Sars-CoV-2 pandemic increased awareness of hyposmia or anosmia, as this can be an accompanying symptom. In mild cases, anosmia without rhinorrhea can be the only presenting symptom of this infection. Timely identification can lead to early detection of otherwise asymptomatic carriers. History taking and essential clinical assessment with appropriate protective measures can be performed in patients in whom COVID-19 is suspected. Patients with anosmia without nasal obstruction should be considered COVID-19 suspect and this should initiate testing or self-isolation. As for treatment of hyposmia or anosmia, the authors do not advise treatment with systemic corticosteroids in patients with COVID-19. Based on expert opinion, nasal corticosteroids can be considered, with a preference for spray formulation. Patients who were already using topical or inhalation corticosteroids for proven pre-existing disease (such as asthma and/or allergy) should be advised to continue their maintenance therapy. ENT (Ear Nose Throat) focus on hyposmia and anosmia should be continued, to gain additional knowledge of the disease mechanisms of COVID-19 and improve follow-up, not only on the pneumological aspects but also to evaluate the impact on quality of life of potentially long-term side effects caused by anosmia.

Keywords: Anosmia, COVID-19, hyposmia, olfactory dysfunction, respiratory tract infection

Introduction on olfactory (dys)function

Olfactory function is part of the chemosensory system and important for digestive behavior as it helps to detect and enjoy food. In addition, it is of importance for social communication and the detection of environmental hazards (1). Processing of olfactory information includes smell receptor stimulation in the olfactory mucosa, adequate neural transmission by the olfactory nerves and processing by the olfactory bulb, parts of the limbic system and the neocortex (2).

Olfactory disorders such as anosmia and hyposmia are estimated to affect 3–20% of the population (1). Apart from aging, three major causative disorders have been identified. Typically, in tertial referral centers these causes include nasal and paranasal sinus disease (21%), infections of the upper respiratory tract (19%), and head trauma (14%). In 22% of patients no identifiable cause is found (3, 4). Other potential causes include neurodegenerative diseases, structural brain disease, toxic chemical exposure, metabolic diseases and side effects of medication or drugs (2, 5). Improvement

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in olfactory function is inversely correlated with the severity and duration of loss of smell, age, smoking, and male sex; up to one-half of patients with olfactory dysfunction improves over time, although for post-traumatic loss improvement is noted only around 10-20% (5). As for (post-)infectious olfactory disorders, the pathophysiology remains poorly delineated, but is thought to involve either damage to the olfactory neuroepithelium (peripheral) or central olfactory processing pathways and can persist in 6-13% of cases (6-11). It was demonstrated that 80% of the patients with post-viral olfactory loss reported subjective recovery after one year, but only 32% reported normosmia; the more favorable prognosis was associated with longer follow-up duration and female gender (12). The varying rates and degree of post-infectious olfactory dysfunction can be explained by the differences in affecting the central olfactory pathways (2, 6).

Depending on the specific cause, standard treatment of olfactory disorders in the course of chronic rhinosinusitis usually includes intranasal corticosteroid and oral corticosteroid treatment. The routine work-up of patients with taste or smell disorders includes a thorough structured history, ENT examination as well as neurologic examination (focusing on cranial nerves I, VII, IX, and X) and additional assessment including computed tomography (CT) and/or brain magnetic resonance imaging (MRI) (5, 13). A well-specified history is also important to distinguish between smell and taste disorders, as complaints of taste loss usually reflect loss of smell function (14). Numerous techniques are available in the clinic for the investigation of chemosensory function and psychophysical testing using orthonasal and retronasal stimulation routes helps to distinguish anosmic from hyposmic patients (15). These psychophysical tests are needed to objectively verify the patient's complaints which can often be misleading (16, 17). Olfactory training appears to be a promising therapy for patients with post-viral olfactory loss to partly regain their sense of smell (18).

COVID-19 and olfactory dysfunction

Currently, the World Health Organization (WHO) has announced a pandemic infection with a previously unknown species of coronavirus, called COVID-19 or SARS-CoV-2. This infection is transmitted mainly through droplets and aerosols, and, causes mild symptoms in the majority of cases. The most common symptoms are fever, dry cough, fatigue, anorexia and myalgia; less common symptoms include headache, sore throat, rhinorrhea, and gastrointestinal symptoms (e.g., nausea and diarrhea) (19). Life-threatening complications of COVID-19 are acute respiratory distress syndrome (ARDS), arrythmia, myocardial injury and shock (20).

Main Points:

- Patients with anosmia without nasal obstruction should be considered COVID-19 suspect and this should initiate testing or self-isolation.
- Based on currently available literature, the authors do not advise treatment with systemic corticosteroids.
- Although there is no evidence-based indication for intranasal corticosteroid, based on expert opinion, the use of intranasal corticosteroids can be considered, with a preference for spray formulation.
- Patients who were already using topical or inhalation corticosteroids for proven pre-existing disease (such as asthma and/or allergy) should be advised to continue their maintenance therapy.
- Follow-up of olfactory function is indicated and olfactory training can be started in cases where olfactory dysfunction persists.

Recent studies report anosmia and dysgeusia as two of the first symptoms of COVID-19 (21, 22). Dysgeusia could be the result of an altered perception of taste caused by the loss of sense of smell, and it might actually point towards a confusion of taste and retronasal olfactory function, i.e. flavor (23, 24). Olfactory dysfunction has been reported as the only symptom in patients with very mild disease. The COVID-19 pandemic has thus led to increased awareness of hyposmia and anosmia, as reports from epicenters show that smell and taste disorders can be first signs of this infection (25-27). There is anecdotal information about the prevalence, onset, and evolution of anosmia, hyposmia and dysgeusia in COVID-19 patients. The first data on anosmia in patients are published by clinicians in the field and spread by special reports of medical associations (21, 28).

In a survey of 59 COVID-19 patients by Giacomelli et al. (29), twenty patients (33.9%) reported at least one taste or olfactory disorder(s) and eleven participants (18.6%) reported both. These authors state that olfactory dysfunction is frequently related to COVID-19 infection and may precede the onset of the disease. The authors refer to the underlying mechanisms as described in mouse models by Netland et al. (30), that demonstrate that SARS-CoV enters the brain primarily via the olfactory bulb, and infection results in rapid, transneuronal spread to connected areas of the brain. Brann et al. (31) reported that ACE-2 receptor, the main host cell receptor of 2019-nCoV playing a crucial role in the entry of virus into the cell to cause the final infection, is expressed on the mucosa of oral cavity and highly enriched in epithelial cells of the tongue. Particularly at the level of the olfactory epithelium, ACE-2 and TMPRSS2 genes are expressed by olfactory sustentacular cells and olfactory stem cells.

Eliezer et al. (32) reported a case where the main symptom expressed by the patient infected by SARS-CoV-2 was the sudden and complete loss of the olfactory function without nasal obstruction. They report that cases of sudden and complete olfactory function loss without nasal obstruction in a patient with other symptoms, such as cough or fever, should alert the clinician to suspect SARS-CoV-2 infection. Vaira et al. (21) report olfactory dysfunction based on history and physical examination in 19.4% out of 320 patients. Kaye et al. reported the initial findings of the anosmia reporting tool on COVID-19 cases for clinicians worldwide (23). Out of 237 entries they noted anosmia prior to COVID-19 diagnosis in 73% while anosmia was the initial symptom in 26.6% of the patients. A recent European multicenter study by Lechien et al. (33) investigated self-reported olfactory dysfunction in 417 mild to moderate COVID-19 cases. Olfactory dysfunction was reported in 85.6% of cases and this occurred in 11.8% before

the presence of other symptoms. Out of the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic.

However, a study from China reported that the ratio of patients complaining of loss of smell and loss of taste was only 5.1% and 5.6% respectively (34). Yan et al. (35) included a total of 1480 patients with influenza-like symptoms that underwent COVID-19 testing. Smell and taste loss were reported in 68% and 71% of COVID-19 positive subjects, respectively, compared to 16% and 17% of COVID-19 negative patients ($p<0.001$). Klopfenstein et al. (36) analysed 114 confirmed COVID-19 patients and the results demonstrated anosmia to be present in 47%, associated with dysgeusia in 85%, of cases. Anosmia was never the first or second symptom to develop, but it was the third symptom in 38% of cases. Anosmia developed 4.4 days after infection onset. The first study using smell quantitative assessment (University of Pennsylvania Smell Identification Test / UPSIT) demonstrated that 98% of COVID-19 patients (n=60) exhibited at least some smell dysfunction. Thirty-five of the 60 patients (58%) were either anosmic (25%) or severely hyposmic (33%) (37). The varying rates might be explained by differences in clinical work-up, specific regional patient characteristics or viral strains.

In the current issue of B-ENT (March 2020), the group of Capelli et al. (38) describes a statistically significant increase in the incidence of hyposmia in the Lombardy city of Codogno, in the epicenter of the COVID-19 outbreak in Italy, in the period between February 21 and March 15, 2020 compared to the incidence of the same symptom in other periods. This and other research will lead to further investigations to determine whether or not hyposmia can be part of the case definition of COVID-19 and what the outcome is after long-term follow-up.

As for the treatment, until now experts and the first reports suggest recovery in the first two weeks after onset of anosmia, but data are still limited. The European Rhinologic Society (ERS) and the ENT UK association advise against giving systemic corticosteroids to patients with sudden olfactory dysfunction since recovery can occur in the first weeks after onset (39, 40). Administering topical nasal corticosteroids in patients with anosmia remains controversial. The ERS and French Agency advocate against the use of nasal corticosteroids in patients with olfactory and gustatory dysfunction without nasal obstruction (40, 41). Although there is no evidence-based indication for intranasal corticosteroid, based on expert opinion, the use of intranasal corticosteroids can be considered, with a preference for spray formulation over gel or drops due to potential viral spill to the lower respiratory tract with the latter formulations. Also based on expert opinion, if topical corticosteroids are considered they should be administered with a long applicator so the olfactory cleft can be reached (42, 43). There can be a role for olfactory training, as it enables improvement of post-infectious olfactory dysfunction in general and it appears to be particularly useful in patients who start it within 12 months after onset (44). A course of topical vitamin A might be considered useful (45). In addition, some experts suggested Zinc as a useful supplement as this is reported to be beneficial to an adequate immune response, can possibly reduce the risk of infection and is investigated for its contribution to olfaction as well (46, 47). Some evidence also suggests the potential usefulness of lipoic acid and omega 3 in the management of olfactory disorders (45, 48).

According to the ENT associations and recent emerging evidence patients presenting with sudden anosmia without nasal obstruction should be considered as COVID-19 suspect (28, 32, 33, 40). Therefore, targeted COVID-19 testing in these subjects could be helpful in diagnosing new Sars-CoV-2 infections. Hereby, asymptomatic carriers could be identified as soon as possible, and viral transmission could be limited. This could also serve as a new criterion for early self-isolation for 1-2 weeks (28, 41, 49).

Recent studies based on a review of treatment of ARDS suggest no benefit from systemic corticosteroids can be expected in COVID-19 cases (50). Because of the immunosuppressive properties mentioned by some, this could lead to prolonged viral replication and worsening of the condition (50, 51). The Centers for Disease Control and Prevention (CDC) and the WHO recommend not giving systemic corticosteroids to patients with COVID-19 pneumonia except for specific case-based indications (e.g., chronic obstructive lung disease exacerbation or septic shock) (19, 52, 53).

According to the ARIA-EEACI (Allergic Rhinitis and its Impact on Asthma & European Academy of Allergy and Clinical Immunology) statement, it is advised to continue intranasal corticosteroids in patients with allergic rhinitis. Even if they become infected by COVID-19, there is no evidence that this could lead to deterioration or a worse outcome. It is also contraindicated to cease intranasal corticosteroids in patients with a common allergy, especially during the spring season, since this could lead to more sneezing and thus easier transmission of the virus in otherwise asymptomatic carriers (54). Several experts (personal communication) have the impression that patients with type 2 helper T (Th2) cells inflammation such as allergic rhinitis (AR) and chronic rhinosinusitis with nasal polyps (CRSwNP) are less prone to infection by COVID-19, with only speculation as to why this may be the case. Furthermore, nasal corticosteroids have been associated with epithelial barrier restoring effects in AR and in CRSwNP, hence rendering the mucosa of individuals less accessible to external harmful triggers such as viruses (55). In addition, a recent study of Zhang et al. reports that patients with allergic diseases or asthma are not at an increased risk for SARS-CoV-2 infection (56). Therefore, the Global Initiative for Asthma (GINA) advises to continue inhaled corticosteroid controller medication. They also recommend continuing prescribed oral corticosteroids in severe asthma and during severe asthma attacks since this could otherwise lead to dangerous situations (57).

Conclusion

The current COVID-19 or Sars-CoV-2 pandemic increased awareness of hyposmia or anosmia, as this can be an accompanying symptom. In mild cases, anosmia without rhinorrhea can be the only presenting symptom of this infection. Timely identification can lead to early detection of otherwise asymptomatic carriers. History taking and essential clinical assessment with appropriate protective measures can be performed

in patients in whom COVID-19 is suspected. Especially in severe COVID-19 cases, key item in the acute setting is without doubt treatment of potentially life-threatening lung disease. As for treatment of hyposmia or anosmia, nasal corticosteroids can be considered. ENT focus on hyposmia and anosmia should be continued, to gain additional knowledge of the disease mechanisms of COVID-19 and improve follow-up, not only on the pneumological aspects but also to evaluate the impact on quality of life of potentially long-term side effects caused by anosmia.

Recommendations

- Based on currently available literature, the authors do not advise treatment with systemic corticosteroids.
- Although there is no evidence-based indication for intranasal corticosteroid, based on expert opinion, the use of intranasal corticosteroids can be considered, with a preference for spray formulation (preferably with a long applicator) over gel or drops due to potential viral spill to the lower respiratory tract with the latter formulations.
- Patients who were already using topical or inhalation corticosteroids for proven pre-existing disease (such as asthma and/or allergy) should be advised to continue their maintenance therapy.
- Based on expert opinion, intranasal vitamin A application can also be considered.
- Patients with anosmia without nasal obstruction should be considered COVID-19 suspect and this should initiate testing or self-isolation.
- Follow-up of olfactory testing is indicated, and olfactory training can be started in cases where olfactory dysfunction persists.

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