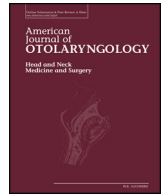




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COVID-19 and anosmia: A review based on up-to-date knowledge

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ABSTRACT

The pandemic of Coronavirus Disease 2019 (COVID-19) has caused a vast disaster throughout the world. There is increasing evidence that olfactory dysfunction can present in COVID-19 patients. Anosmia can occur alone or can be accompanied by other symptoms of COVID-19, such as a dry cough. However, the pathogenic mechanism of olfactory dysfunction and its clinical characteristics in patients with COVID-19 remains unclear. Multiple cross-sectional studies have demonstrated that the incidence rate of olfactory dysfunction in COVID-19 patients varies from 33.9–68% with female dominance. Anosmia and dysgeusia are often comorbid in COVID-19 patients. Otolaryngologists should be mindful of the symptom of anosmia in outpatients so as not to delay the diagnosis of COVID-19. In this paper, we have reviewed the relevant knowledge based on up-to-date literature.

1. Introduction

In December 2019, Coronavirus Disease 2019 (COVID-19) outbreak occurred in Wuhan, Hubei Province, China and spread rapidly throughout China, and then emerged around the world [1–3]. On February 12, 2020, (World Health Organization) WHO named the disease caused by the novel coronavirus as COVID-19 [4]. Clinical evidence has shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be transmitted by person-to-person [1]. Recently, the number of COVID-19 cases has skyrocketed worldwide. As of May 3, 2020, WHO reports that 3,349,786 people have been diagnosed with COVID-19 worldwide, with 238,628 deaths, including 214 countries and territories [3]. COVID-19 pandemic has had a massive impact on global health-care systems and economic stability.

In COVID-19 patients, the main manifestations were fever and cough and characterized by lymphocytopenia and ground-glass opacity changes on chest computed tomography [2]. Patients with severe infection can also develop neurological manifestations such as acute cerebrovascular diseases, skeletal muscle injury and impaired consciousness [5]. Besides, some patients may present with upper respiratory symptoms such as pharyngodynia, sore throat, nasal congestion, rhinorrhea and olfaction alterations [6,7]. Olfactory dysfunction (OD), including anosmia and hyposmia, manifests itself particularly prominently among these symptoms in COVID-19 patients [8].

However, the extent of potential OD manifestation of COVID-19 has remained unclear.

To clarify the relationship between OD and COVID-19, we have broadly searched literature databases, including PubMed, Google Scholar, Web of Science and Centers for Disease Control and Prevention (CDC). To get updated study information, we also explored the preprints database (Medrxiv, Biorxiv) and manually browsed the homepages of some otolaryngology journals. This review summarizes the study published on OD during the COVID-19 pandemic and to explore its mechanisms of occurrence and coping strategies.

2. SARS-CoV-2 and the nasal cavity

There are seven coronaviruses known to cause infection in humans, in addition to SARS-CoV-2, and six others such as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1 [9]. The genome sequence of SARS-CoV-2 is a 29,903 bp single-stranded RNA coronavirus [10]. SARS-CoV-2 and SARS-CoV belong to the β -genus of the coronavirus family and share 82% similarity in gene sequence [11].

SARS-CoV-2 virus employs the spiny protein S1, which makes the virion adhere to the cell membrane by interacting with the host ACE2 receptor [10]. ACE2 is a functional receptor for SARS-CoV-2, and its

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expression and distribution in the nervous system suggest that SARS-CoV-2 can cause neurological manifestations through direct or indirect pathways [5]. Due to the unique anatomy of the olfactory system, including the olfactory bulb and olfactory nerve, viruses can also contribute to central nervous system infections via the cribriform plate [12,13].

Multiple pieces of evidence confirmed that the nasal cavity is a vital area susceptible to SARS-CoV-2 infection. Using rhesus macaques model of coronavirus infection, the researchers compared the pathology and virology of SARS-CoV-2, SARS-CoV and MERS-CoV [14]. The study revealed that these pathogenic coronaviruses have different mainly pathogenic sites: SARS-CoV-2 (nose and throat); SARS-CoV (lung); MERS-CoV (type II pneumocytes) [14]. Viral loads in the patient's nasal cavity were higher than the viral loads in the pharynx, both symptomatic individuals and asymptomatic ones, hinting the nasal cavity as the first gateway for the initial infection [15]. The researchers investigated the expression of SARS-CoV-2 entry-associated genes, ACE2 and TMPRSS2, in single-cell RNA-sequencing datasets from different tissues in the human body [16]. Goblet cells and ciliated cells in the nasal mucosa may be the initial site of SARS-CoV-2 infection, implicating primary SARS-CoV-2 transmission is through infectious droplets [16]. Furthermore, SARS-CoV-2 was detected in the tears of COVID-19 patient and can cause nasal infection via the nasolacrimal duct [17,18]. Therefore, these findings could explain the highly infectious and highly pathogenic nature of COVID-19.

Anosmia is defined as the absence of all OD, which can be caused by a variety of causes, with upper respiratory tract infections being a frequent cause [19]. Among the various pathogens, the most common is the virus, and coronavirus is one of them [19,20]. Coronavirus 229E, a common cold variant, has been shown cause hyposmia for human subjects [21]. Anosmia caused by SARS-CoV has been reported during the SARS epidemic [22]. However, the incidence of anosmia caused by SARS-CoV-2 may be much higher than that of SARS-CoV. Post-infectious OD is thought to be caused by damage to the olfactory epithelium or central olfactory processing pathways [19].

3. The association between OD and COVID-19

Aggregating shreds of evidence suggests that OD is one of the most common signs of COVID-19 [23]. The symptom of OD has caught the attention of otolaryngologists all over the world during the COVID-19 pandemic. There is a growing body of research on this issue. Here, we have summarized the studies published from late March to May 1 (Table 1).

Anosmia is a prominent sign of SARS-CoV-2 infection [24]. Patients with COVID-19 can present a sudden onset of anosmia without any other symptoms [24,25]. Before the onset of anosmia, other mild symptoms such as a dry cough may also be presented [26]. In a retrospective study by Klopfenstein et al., 54 (47%) out of 114 confirmed COVID-19 patients presented with anosmia [27]. The study also found that patients generally developed anosmia 4.4 days after the onset of the SARS-CoV-2 infection, with a duration of 8.96 days, and 98% of patients could recover within 28 days [27]. OD often accompanied by dysgeusia in COVID-19 patients [27,28].

Several cross-sectional studies about the prevalence rate of OD in COVID-19 patients have been released, including in countries such as Italy, Spain, the United Kingdom, France, Belgium, the United States and Iran [29–33]. These surveys were typically handled through non-contact methods such as online questionnaires and telephone interviews [23,30,33]. Incidence of OD in COVID-19 patients varied widely among these cross-sectional studies, with rates ranging from 33.9 to 68% [29–33]. The studies showed that individuals with smell disorders tend to have a taste disorder, suggesting a probable association between the two [29–33]. Also, most studies have found that the incidence of smell disorders in COVID-19 patients is higher in females than males [29,30,33]. The characteristic of female preponderance is consistent

with the findings of previous studies about the OD caused by upper respiratory infection [34].

To date, two case-control studies on the relationship between OD and COVID-19 have been carried out [35,36]. Moein et al. performed the olfactory function test (OFT) of 60 SARS-CoV-2 positive patients and took 60 subjects from previous studies as a control group matching the age and gender of the patient's group [35]. The study revealed that the COVID-19 patients presented a pronounced OD, matched the control group and the published normative data [35]. Another investigation, using a self-reported questionnaire, analyzed the prevalence of smell and/or taste disorders in COVID-19 patients and influenza patients [36]. It proved that the incidence rate in COVID-19 patients was significantly higher than that in influenza patients at 39.2% and 12.5%, respectively [36]. A limitation of this study is the absence of OFT, only relying on a questionnaire, which can contribute to the bias of the results.

OFT has been the mainstay for diagnosis of OD; however, the patients in most studies were untested by OFT. So far, OFT was available only in several studies [35,37,38]. Marchese-Ragona et al. reported that hyposmia was the sole or primary symptom in six COVID-19 patients, confirmed by six odours smell test called “le nez du vin” [37]. Moein et al. first conducted a 1:1 matched case-control study, administering the 40-odorant University of Pennsylvania Smell Identification Test, to focus on the associations between OD and COVID-19 inpatients [35]. The study found that 59(98%) out of 60 COVID-19 subjects exhibited some OD, only 21 (35%) of them were aware before testing, revealing the exact incidence is much higher than the self-reported rate [35]. Notably, this study provided firm evidence that OD is often associated with COVID-19. Vaira et al. performed a remote olfactory evaluation for 23 COVID-19 patients in-home quarantine, utilizing patient self-administered OFT with a decreasing concentration of denatured ethyl alcohol solution [38]. The data of the patient self-administered OFT can help the early detection and isolation of COVID-19 patient [38].

Mayo Clinic used artificial intelligence with the most advanced deep neural networks technology to identify and analyze the clinical features of SARS-CoV-2 infection [39]. The study found that the prevalence of anosmia/dysgeusia in COVID-19-positive patients was 28.6-fold that of COVID-19-negative patients and anosmia/dysgeusia was one of the earliest signatures of COVID-19 [39]. Susceptibility to SARS-CoV-2 infection is influenced to some degree by host genotype; the heritability for anosmia was 47 (95% confidence intervals 27–67)% [40].

Google Trends (GT), an excellent internet-based tool, has been applied to medical research in otolaryngology in recent years [41]. During the COVID-19 outbreak, GT related to olfactory disorders has abnormally elevated in multiple countries [25,42]. Gane et al. study the GT for the “anosmia” topic from October 2019 to Mar 23, 2020, for the United Kingdom (UK), the United States (US), and Italy [25]. They concluded that the curves of GT have significant fluctuations in all three countries during the epidemic, with most notably in the UK [25]. Another similar research carried out by Walker et al. explored the internet activity about the loss of smell in UK, France, Germany, Italy, Netherlands, Spain, Iran and the US [42]. The study revealed a strong correlation between daily relative search volumes related to anosmia and the onset numbers of COVID-19 patients in these countries [42]. Unfortunately, there were no GT data about China available in the literature because of the access restrictions.

Based on the current research, OD has a high incidence rate in COVID-19 patients in some European and American countries, while it rarely occurs in Chinese patients [7,27]. Lovato and de Filippis reviewed five articles about the clinical presentation of COVID-19 patients from China, comprising 1556 cases, with no reports of OD [7]. Mao et al. retrospectively analyzed the neurologic symptoms of 214 patients in Wuhan, China, and found that 5.1% (n = 11) of the patients exhibited smell impairment [5]. To our knowledge, this paper is the only study to date to describe OD with COVID-19 patients in China.

Several reasons are accounting for the incidence of OD with patients

Table 1
Summary of the literature on the association between olfactory dysfunction and COVID-19.

No.	Publication date	Authors	Country	Study methods	Number of patients	Age (Mean ±)	Diagnosis methods	Prevalence rate/(n =)	Female preponderance	Dysgeusia-related
01	March 26	Giacomelli et al. [29]	Italy	Cross-sectional	59	Unknown	Questionnaire	33.9% (n = 20)	Yes	Yes
02	March 27	Bagheri et al. [30]*	Iran	Cross-sectional	10,069	32.5 ± 8.6	Questionnaire	48.23% (n = 4856)	Yes	Yes
03	April 1	Vaira et al. [53]	Italy	Retrospective	320	Unknown	Self-reported	19.4% (n = 62)	Unknown	Yes
04	April 2	Gane et al. [25]	United Kingdom	Case report	1	48	Self-reported			No
05	April 3	Villalba et al. [54]	France	Case series	2	82.5	Self-reported			Yes
06	April 5	Hjelmseth and Skaare [55]	Norway	Case series	3	Unknown	Self-reported			Yes
07	April 6	Lechien et al. [23]	European countries▲	Multicenter	417	36.9 ± 11.4	Questionnaire	85.6% (n = 357)	Yes	Yes
08	April 7	Menni et al. [31]	United Kingdom	Cross-sectional	579	40.79 ± 11.84	Community survey	59.41% (n = 344)	Yes	Yes
09	April 8	Eliezer et al. [26]	France	Case report	1	40s	Five odorants test★			No
10	April 12	Yan et al. [32]	United States	Cross-sectional	59	Unknown	Self-reported	68% (n = 40)	Unknown	Yes
11	April 16	Klopfenstein et al. [27]	France	Retrospective	114	47 ± 16	Self-reported	47% (n = 54)	Yes	Yes
12	April 17	Moein et al. [35]	Iran	Case-control	60	46.55 ± 12.17	UPSIT★★	98.33% (n = 59)	No	Unknown
13	April 22	Spinato et al. [33]	United Kingdom	Cross-sectional	202	56 ± 11	Telephone interviews	64.4% (n = 130)	Yes	Yes
14	April 22	Heidari et al. [24]	Iran	Case series	23	37.4	Self-reported	69.57% (n = 16)	Yes	Unknown
15	April 22	Beltran-Corbellini et al. [36]	Spain	Case-control	79	52.6 ± 17	Self-reported	31.65% (n = 25)	Unknown	Yes
16	April 24	Yan et al. [56]	United States	Retrospective	169	53.5	Self-reported	75.7% (n = 128)	Unknown	Yes
17	April 27	Ottaviano et al. [37]	Italy	Case series	6	Unknown	Le nez du vin★★★		Unknown	Unknown
18	April 28	Kaye et al. [57]	Multiple countries▲▲	Reporting tool	237	39.6 ± 14.6	Self-reported		Yes	Unknown
19	April 29	Gilani et al. [58]	Iran	Case series	5	35.6	Self-reported		Yes	Unknown
20	May 1	Luers et al. [28]	Germany	Retrospective	72	38 ± 13	Self-reported	74% (n = 53)	No	Yes
21	May 1	Vaira et al. [38]	Italy	Case series	33	51.8	Self-tested	75.8% (n = 25)	Yes	Yes

Notes: *Patients who have not been confirmed by laboratory tests; ▲ European countries: Including Belgium, France, Spain and Italy; ▲▲ Multiple countries: Including United States, Mexico, Italy, UK and Other.
★ Five odorants test: phenyl-ethyl-alcohol, cyclohexene, isovaleric acid, undecalactone, and skatole; ★★ UPSIT: University of Pennsylvania Smell Identification Test; ★★★ le nez du vin: a quick test method of olfaction.

differs in different countries. First, SARS-CoV-2 can produce mutations capable and develop its pathogenicity [43]. Forster et al. conducted a phylogenetic network analysis of SARS-CoV-2 genomes and found three central variants with the remarkably changed amino acid [44]. The A and C genotype of SARS-Cov-2 have significant proportions in Europeans and Americans; however, the B type is the most common genotype in East Asian [44]. Type A and C strains are speculated to be high pathogenicity for the nasal cavity of human, resulting in an increased prevalence of olfactory disorders in European and American countries. Second, pathogenic susceptibility to SARS-CoV-2 may also vary among different human species. However, evidence to support this speculation is absent. Third, because of COVID-19 outbreak initially occurred in China, doctors were not sufficiently aware of the disease, recognizing only the primary life-threatening symptoms but overlooking the olfactory manifestation. OD is also one symptom that the patient is the most workable to overlook. However, the specific reasons for this difference still need to be further studied in the future.

4. Response from professional organizations

Many professional organizations have recognized that COVID-19 patients may have the symptom of OD and have included this symptom in their COVID-19 diagnostic guidelines, or issued a warning to the public. On March 21, Prof Claire Hopkins, President of the British Rhinological Society, first officially emphasized anosmia as a common early symptom of COVID-19 infection [45]. On March 26, American academy of otolaryngology-head and neck surgery released a statement noting that anosmia with dysgeusia is a symptom associated with the COVID-19 patients [46]. The academy has also established the COVID-19 Anosmia Reporting Tool, an online questionnaire, for patients globally to submit data [46]. On April 17, CDC summarized and updated the most common symptoms of COVID-19, adding “new loss of taste or smell” to the list of symptoms [47]. Similarly, neurologic symptoms, including anosmia, also have attracted the attention of neurologists [48].

5. Coping strategies for otolaryngologists

As anosmia could be the sole clinical presentation of COVID-19 patients without any other significant signs, it pushes otolaryngologist to the forefront [24]. Otolaryngologists should always be vigilant when dealing with outpatients so as not to delay COVID-19 diagnosis. To avoid cross-infection, the otolaryngologist may consider a remote olfactory evaluation for COVID-19 patient with OD [38]. Laboratory testing and self-isolation are needed for patients who exhibit anosmia.

Otolaryngology is a high-risk department for COVID-19, especially for the otolaryngologists over 60 [49]. In this battle, it is especially important for medical personnel to do their personal protection [50]. Researchers detected the high concentration of SARS-CoV-2 RNA in aerosols in some public areas of two Wuhan hospitals during the COVID-19 outbreak [51]. They suggested that SARS-CoV-2 may have the potential to transmit via aerosols [51]. Except for emergency illnesses, online telemedicine in otolaryngology is a good option for reducing COVID-19 cross-infection [52].

6. Current confusion and future directions

The destructive power and the exact mechanism of the SARS-CoV-2 on the olfactory system remain unknown. The current research and evidence are fragmented and unsystematic; the understanding between OD and COVID-19 is still far from enough. Except for inflammatory blockage of the olfactory cleft existed in one patient in a case report literature, CT imaging data of the nasal cavity and sinus was not available in the rest of the studies. It is unclear whether the OD result from viral-induced olfactory nerve damage or local inflammation of the nasal cavity or both. These current studies lack the longitudinal results

of olfactory changes of the COVID-19 patients, from onset to complete recovery. Therefore, whether OD with COVID-19 patient is temporary or permanent remains to be elucidated. What is the exact prevalence of OD in COVID-19 patients globally? Can OD be used as a valuable indicator of the diagnosis and prognosis of COVID-19 patients?

More extensive studies, both basic and clinical, would need to be conducted to unveil these mysteries in the future. The similarity to humans being, the SARS-CoV-2 infection rhesus monkey can be used to study the pathological and physiological of the olfactory system. The olfactory epithelium can be biopsied from the COVID-19 patient for ultrastructural observation to better understand the pathology of OD in COVID-19 patients [34]. After containing the COVID-19 pandemic, the multicenter epidemiological investigation, including different countries and races, should be carried out.

7. Limitations

Limitations in the original researches also yield limitations of the present review. In some cross-sectional studies, patients were identified by the reported questionnaire submitted by themselves, which were not verified by the researchers. OD was based on self-report rather than OFT in most studies. Besides, some essential information, such as gender and age, did not appear in some studies. For covering the latest knowledge, this review also uses data from several preprints literature that has not been undergone full peer review.

8. Conclusions

OD is a characteristic sign of COVID-19 patient, which can occur independently or with other symptoms, but its pathogenesis is not well understood. In-depth studies are needed to elucidate clinical features and pathogenesis of COVID-19 patient with OD. Otolaryngologists should be aware of anosmia to avoid delaying the diagnosis of COVID-19 and thus contributing to an epidemic.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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Declaration of competing interest

The authors declare that they have no competing interests.

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