Smell disorders associated with COVID-19 infection

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Abstract

Background: We performed a search in the PubMed databases, Web of Science, LILACS, MEDLINE, SciELO, and Cochrane Library using the keywords COVID-19, Novel coronavirus, corona, 2019-nCoV, SARS-CoV-2, ENT, nose, anosmia, hyposmia, smell, olfactory, ORL, different ENT related symptoms. We reviewed published and peer-reviewed studies that reported the ENT manifestations in COVID-19 laboratory-confirmed positive patients.

Main text: Within the included 2549 COVID-19 laboratory-confirmed positive patients, smell affection was reported in 1453 patients (57%). The other reported ENT manifestations were taste disorder (49.2%), headache (42.8%), nasal blockage (26.3%), sore throat (25.7%), runny nose or rhinorrhea (21.3%), upper respiratory tract infection (URTI) (7.9%), and frequent sneezing (3.6%).

Conclusion: Smell affection in COVID-19 is common and could be one of the red flag signs in COVID-19 infection. With a sensitivity of utilized questionnaire in smell identification, a homogenous universal well-defined COVID-19 questionnaire is needed to make the COVID-19 data collection more sensible.

Keywords: COVID-19, Coronavirus, Anosmia, Hyposmia, Smell, Olfactory, ENT, Otorhinolaryngology

Background

At December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially known as the 2019 novel coronavirus (2019-nCoV), started in China in Wuhan [1, 2]. Since that moment, this novel virus, also named as coronavirus disease 2019 (COVID-19), has crossed all countries’ borders with dramatic spread all over the world till the World Health Organization (WHO) defined it as a pandemic disease on March 11, 2020.

The COVID-19 is part of the species of the SARS-related coronaviruses that over the last two decades have led to preceding epidemics as SARS-CoV in China in 2002–2003 [3] and the Middle East Respiratory Syndrome (MERS-CoV) in Saudi Arabia in 2012–2013 [4].

The novel COVID-19 is presented mainly by lower respiratory tract-related manifestations such as fever, cough, dyspnea, and chest tightness that could progress quickly to acute respiratory distress syndrome (ARDS) [5]. However, COVID-19 leads as well to different upper respiratory tract-related manifestations comprising sore throat, smell dysfunction, and nasal congestion [6].

The available data on the ear nose throat (ENT) manifestations of COVID-19 is recently published [7] and review studies on smell in COVID-19-positive patients are still growing.

Smell and taste dysfunctions in COVID-19 patients were sparsely cited in the literature and there is still a paucity of peer-reviewed publications to support a causal association between COVID-19 and anosmia [7, 8].

Thus, the aim of the current work was to detect and discuss the smell disorders associated with confirmed COVID-19 infection in the reviewed and published literature.

Main text

Methods

We searched several medical databases, including PubMed databases, Web of Science, LILACS, MEDLINE, SciELO, and Cochrane Library using the keywords COVID-19, Novel coronavirus, corona, 2019-nCoV, SARS-CoV-2, ENT, nose, anosmia, hyposmia, smell, olfactory, ORL, different ENT related symptoms. We reviewed published and peer-reviewed studies that reported the ENT manifestations in COVID-19 laboratory-confirmed positive patients.
Smell identification tests were University Of Pennsylvania was used in 172 patients (11.8%). The utilized smell in most patients (1281 patients, 88.2%), while smell test recover (Fig. 1). Other hand, in 242 patients (26.3%), smell did not recovery was detected in 121 patients (13.2%). On the was reported in 556 patients (60.5%), while late (partial) was defined as anosmia in 376 patients (58%), in 336 patients (22.2%), arthralgia/myalgia in 674 patients (57.4%), cough in 1058 patients (69.8%), dyspnea in 336 patients (22.2%), arthralgia/myalgia in 674 patients (44.5%), asthenia/fatigue in 556 patients (36.7%), and loss of appetite in 414 patients (27.3%) (Fig. 3).

Discussion

A novel coronavirus (CoV) epidemic, produced by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), began in December 2019 from China [4, 7]. On February 11, 2020, the WHO named the disease caused by this novel virus as COVID-19. The widespread transmission and infectivity of COVID-19 marks it as a significant pathogen with a considerable health threat [32].

COVID-19 manifests with a wide clinical range extending from no symptoms to multi-organ dysfunctions and septic shock. Despite its rapid distribution worldwide, the clinical features of COVID-19 remain to a variable extent non-specific [6–8, 32].

The nasal, nasopharyngeal, and/or the oropharyngeal tissues are part of the main harbor locations of the infection, main site of sample taking for testing, and a main
Table 1 All included studies discussing olfactory dysfunction with COVID-19

| Article                  | Publish date | Type or article                  | COVID-19 (M/F) | COVID-positive patient with smell disorder | Percentage | Smell identification | Notes |
|-------------------------|--------------|----------------------------------|----------------|--------------------------------------------|------------|---------------------|-------|
|                         |              |                                  |                | Smell disorder                             |            |                     |       |
|                         |              |                                  |                | Anosmia Hyposmia Dysosmia                   |            |                     |       |
| 1 Giacomelli et al [9]  | Mar 2020     | Cross-sectional study            | 59(40/19)      | 17 Unknown                                 | 28.8%      | Questionnaire       |       |
| 2 Vaira et al [10]      | Apr 2020     | Rapid communication paper        | 320            | 62 Unknown                                 | 19.4%      | Questionnaire       |       |
| 3 Villalba et al [11]   | Apr 2020     | Case series                      | 2(1/1)         | 2 Unknown                                  | 100%       | Questionnaire       |       |
| 4 Hjelmesæth et al [12] | Apr 2020     | Case series                      | 3 (2/1)        | 3 Unknown                                  | 100%       | Questionnaire       |       |
| 5 Lechien et al [13]    | Apr 2020     | Cross-sectional multicenter study | 417 (154/263)  | 357 284 73                                 | 85.6%      | Questionnaire       |       |
| 6 Mao et al [14]        | Apr 2020     | Retrospective study              | 214 (87/127)   | 11 Unknown                                 | 5.1%       | Questionnaire       |       |
| 7 Gilani et al [15]     | Apr 2020     | Case series                      | 5 (2/3)        | 5 Unknown                                  | 100%       | Questionnaire       |       |
| 8 Eliezer et al [16]    | Apr 2020     | Case report                       | 1 (0/1)        | 1 Unknown                                  | 100%       | CCCRC               |       |
|                         |              |                                  |                |                                            |            | CT scan of the nasal cavity showed bilateral inflammatory obstruction of the olfactory clefts that was confirmed on MRI of the nasal cavity. There were no anomalies of the olfactory bulbs and tracts. |       |
| 9 Yan et al [17]        | Apr 2020     | Cross-sectional study            | 59 (29/29/1)   | 40 Unknown                                 | 67.8%      | Questionnaire       |       |
| 10 Klopfenstein et al [18] | Apr 2020 | Retrospective study              | 144            | 54 Unknown                                 | 37.5%      | Questionnaire       |       |
| 11 Moein et al [19]     | Apr 2020     | Case-control study               | 60 (20/40)     | 59 15 44                                   | 98.3%      | UPSIT<sup>1</sup>   |       |
| 12 Spinato et al [20]   | Apr 2020     | Cross-sectional study            | 202 (97/105)   | 130 48 82                                  | 64.4%      | Questionnaire       |       |
| 13 Beltrán-Corbellini et al [21] | Apr 2020 | Case-control study               | 79             | 25 14 9 2                                  | 31.6%      | Questionnaire       |       |
| 14 Yan et al [22]       | Apr 2020     | Retrospective study              | 128 (61/67)    | 75 Unknown                                 | 58.6%      | Questionnaire       |       |
| 15 Kaye et al [23]      | Apr 2020     | Short communication study        | 237 (108/129)  | 237 Unknown                                | 100%       | Questionnaire       |       |
| 16 Ottaviano et al [24] | Apr 2020     | Case series                      | 6              | 6 Unknown                                  | 100%       | Le Nez du Vin<sup>2</sup> |       |
| Article | Publish date | Type or article | COVID-19 (M/F) | COVID-positive patient with smell disorder | Percentage | Smell identification | Notes |
|---------|--------------|----------------|---------------|------------------------------------------|------------|----------------------|-------|
| 17 Heidari et al [25] | Apr 2020 | Case series | 23 (8/15) | 23 | Unknown | 100% | Questionnaire |
| 18 Kim et al [26] | May 2020 | Cross-sectional study | 172 (66/106) | 68 | Unknown | 39.5% | Questionnaire |
| 19 Boscolo-Rizzo et al [27] | May 2020 | Cross-sectional study | 54 | 34 | Unknown | 63% | Questionnaire, Comparison between probability of acute smell loss in COVID-19 and normal individual |
| 20 Luers et al [28] | May 2020 | Retrospective study | 72 (41/31) | 53 | Unknown | 73.6% | Questionnaire |
| 21 Vaira et al [29] | May 2020 | Cross-sectional study | 33 (11/22) | 17 | 13 | 4 | 51.5% | CCCRCb |
| 22 Vaira et al [30] | Jun 2020 | Cross-sectional study | 72 (27/45) | 61 | 2 | 58 | 84.7% | CCCRCb, Smell disorder identification by history 44 patients / by test 61 patients |
| 23 Boscolo-Rizzo et al [31] | Jul 2020 | Cross-sectional study | 187 (84/103) | 113 | Unknown | 60.4% | Questionnaire |
| | | | | | | | |
| | | | | | | |
| 2549 M = 838 |
| F = 1107 |
| Unknown = 603 |
| Gender diverse = 1 |

aUniversity of Pennsylvania Smell Identification Test (UPSIT)
bConnecticut Chemosensory Clinical Research Center (CCCRC) orthonasal olfaction test'
cLe Nez du Vin = six supra-threshold odors forced multiple choice smell identification test
source of infection transmission. However, most COVID-19 published studies are focused on the lower respiratory tract manifestation and sequel because of their life-threatening potentiality [7, 32].

Meanwhile, the literature on ENT manifestation during COVID-19 infection remains growing. Thus, there is value in studying smell dysfunction and other ENT manifestations of such novel virus and there is a need to recognize the defining smell dysfunction epidemiological and clinical characteristics in COVID-19 with more precision.

In the current review of literature, we tried to collect the data concerning the smell disorders associated with laboratory-confirmed COVID-19 cases in only the peer-reviewed and published papers to provide an up-to-date delineation of the olfactory clinical characteristics and incidence in COVID-19 patients to help ENT and other physicians dealing with COVID-19 to understand and approach such cases and assist in data building up for this novel disease.

The results of the current study agree with previous reports [6–8] that fever (recounted in 57.4% of the included patients) and cough (reported in 69.8%) are the principal symptoms of COVID-19 whereas gastrointestinal and ENT symptoms were less common, suggesting the difference in viral tropism as compared with influenza, SARS-CoV, and MERS-CoV [4, 21].

In the current study, the percentage of COVID-19 patients complaining of smell disorder was about 57% with the fact that questionnaire as a tool in smell identification with poor sensitivity value 65.6%. The most common ENT manifestation of COVID-19 in descending order were smell dysfunction (55.6%), taste disorder (49.2%), headache (42.8%), nasal congestion and blockage (26.3%), and sore throat (25.7%). On the other hand, the most prevalent associated general symptoms in relation to smell and taste disorder in descending order were cough (69.8%), fever (57.4%), arthralgia/myalgia (44.5%), asthenia/fatigue (36.7%), loss of appetite (27.3%), and dyspnea (22.2%).

Degree of smell affection shows variability, anosmia accounts to about 58%, while hyposmia about 41.6%.

About 28.3% of affected patients complained of early smell affection as the only or first presentation with only 0.9% possibility of progression to severe or critical COVID-19. Late smell affection occurred 3–5 days after

![Fig. 1 Onset/offset of smell disorder with COVID-19 patients; onset (early-late)—offset (complete recovery-partial recovery-persistent smell disorder)](image)

![Fig. 2 ENT symptomatology of COVID-19](image)
common acute respiratory tract infection in about 71.7%.

Even though smell recovered in most cases (73.7%) whether early recovery (within 2 weeks, 60.5%) or later recovery (13.2%), smell did not recover in more than one quarter of the patients (26.3%). No specific regimen was associated with olfaction recovery. Vitamin, omega-3, and trace elements with nasal steroid were prescribed without evidence of superiority of certain medication. Olfaction recovery was reported even without medication. This must be discussed with the patients and the physicians and also there is a need to evaluate the used therapy in those patients and its effect on the smell recovery. Also the viral strain as director of the prognosis is another question.

As an overall view regarding the severity of COVID-19 and smell disorder, in less than 5% of the smell-affected patients, the COVID-19 was severe or critical. This may reflect no association between disease severity and smell affection, but smell disorder could be masked by both respiratory and critical manifestations in those severe and critical COVID-19 patients.

Post-viral anosmia is a widespread cause of adult smell dysfunction (40% of anosmia cases). Viruses that induce the common cold or upper respiratory tract infections are well known to lead to post-infectious smell loss. The previously defined corona viruses are assumed to account for 10–15% cases [33]. This novel viral infection seems to affect smell sensation over other viruses. Odds ratio describing likelihood of COVID-19 associated with smell disorder is over that of influenza virus by 4.5 folds [21]. Moreover, acute smell dysfunction is reported in COVID-19 infection over normal persons by 13.2 times (odds ratio of smell disorder in normal and COVID-19-positive persons in two studies) with exclusion of obstructive olfactory disorder [17, 27].

Smell and taste dysfunctions were sparsely declared in the COVID-19 literature, and there is still a lack of peer-reviewed literature to support a causal association between COVID-19 and anosmia [6–8]. Olfactory neuritis is the most accepted theory of smell disorder but some studies emphasize on the presence of inflammatory change in olfactory cleft to be more than the changes affecting the olfactory neural pathway which is clearly detected by radiological studies like CT-MRI [16].

In peer-reviewed studies apart from case reports, smell dysfunction showed wide variation, with high records of 98.3% [19] and 85.6% [13] and low percentage of 5.1% [14] and 19.4% [10] respectively. However, they utilized a questionnaire focused on the psychological and social burden of the smell disorders, particularly with the COVID-19 pandemic scenario and the following social life restrictions, which might result in overestimation [13].

In the current review, smell affection was detected in 57% of included patients. Most COVID-19 studies particularly at the primary spread of the disease from December 2019 to March 2020 did not mention the smell affection particularly the early and primary reports, and most COVID-19 patients (66%) reported a complete recovery of their chemosensitive functions during the disease course [23].

Zhang et al [34] recommend considering patients who complained of anosmia without runny nose or nasal obstruction COVID-19 suspicion and recommending starting testing or self-isolation for those patients.

Limitations
Because of the rapid serious health emergency of COVID-19, data collection and analysis are very difficult due to incomplete documentation lacking universal accurate description of the clinical manifestations without using a universal questionnaire for those patients. In addition, most COVID-19 studies missed asymptomatic or mild confirmed cases managed at home and there is very limited available ENT endoscopic or radiological...
data in COVID-19 published papers. All these mentioned limitations are features of the published researches on COVID-19 up till now and should be taken into consideration in future research. Moreover, most smell affection was evaluated via a questionnaire and patients were identified by the reported questionnaire submitted by themselves, which were not verified by the researchers. Besides, some essential information, such as gender and age, did not appear in some studies and previous history of smell disorders and nasal diseases and/or nasal examination was not mostly mentioned. Many early COVID-19 studies did not ask about or test for smell disorders, and early questionnaire and/or checklist did not include smell disorders. Therefore, all included studies in the current review were published after March 2020. Chinese studies showed less smell mention that may be attributed to less doctors, patients, and community orientation about the condition or presence of different viral strains

Thus, we agree with El-Anwar et al [7] that a standard worldwide questionnaire for definite COVID-19 manifestations is required to make the COVID-19 data well defined, homogenous, and complete in order to deliver insights of diagnostic features of the common COVID-19 manifestations. Thus, otolaryngologists should be mindful of the symptom of anosmia in outpatients so as not to delay the diagnosis of COVID-19.

It is highly recommended to re-assess the recovered COVID-19 patients who become negative for late disease sequels including the smell examination and nose radiology since the late sequels of the COVID-19 infection after being negative need also to be assessed. Pathogenesis is not well understood, study of olfactory bulb size in those patients may point to the pathogenesis.

Otolaryngologists, physicians, patients, and the community should be aware of anosmia to avoid delaying the diagnosis of COVID-19 and thus contributing to an epidemic.

Conclusions

Olfactory manifestations for COVID-19 are common and should be added to suspected clinical criteria of COVID-19 particularly if nasal examination was non-significant. However, a standard universal questionnaire by well-defined COVID-19 manifestations is needed to make the COVID-19 data accurately defined, homogenous, and complete.

Acknowledgements
No one has to be acknowledged—every participant is included as author with no financial support.

Authors’ contributions
ME, data collection, statistical analysis, manuscript writing and formatting, manuscript revision. SM, data collection – literature review, manuscript writing, manuscript formatting. AS, triggering the idea, data collection – literature review, statistical analysis, manuscript writing and formatting, submission procedure. All authors have read and approved the manuscript.

Funding
No financial support

Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations
Ethics approval and consent to participate
Not applicable—review article.

Consent for publication
Not applicable—review article.

Competing interests
No conflict of interest.

Received: 27 August 2020 Accepted: 5 April 2021
Published online: 01 May 2021

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