ACTA OTORHINOLARYNGOLOGICA ITALICA 2020;40:241-247; doi: 10.14639/0392-100X-N0862

Review

Loss of smell in COVID-19 patients: a critical review with emphasis on the use of olfactory tests

COVID-19 e olfatto: revisione critica della letteratura sulla valutazione olfattiva

Rosario Marchese-Ragona[1], Domenico Antonio Restivo[2], Eugenio De Corso[3], Andrea Vianello[4], Piero Nicolai[1], Giancarlo Ottaviano[1]

[1] Department of Neuroscience, Otolaryngology Section, University of Padua, Italy; [2] Department of Medicine, Neurological Unit and Service of Clinical Neurophysiology, Garibaldi Hospital, Catania, Italy; [3] Fondazione Policlinico Universitario A. Gemelli IRCCS, Unità Operativa di Otorinolaringoiatria, Università Cattolica del Sacro Cuore, Rome, Italy; [4] Department of Cardiological, Thoracic and Vascular Sciences, Respiratory Pathophysiology Unit, University of Padua, Italy

SUMMARY

Since December 2019, an outbreak of a newly isolated coronavirus (SARS-CoV-2) appeared in Wuhan, China, and then spread worldwide. Recently, it has emerged that a number of patients may present with sudden hyposmia, sometimes without other symptoms of the disease. We performed a critical review on the methods used to date to investigate the olfactory function in COVID-19 patients in order to establish which should be considered the most appropriate to use during this pandemic. Literature analysis showed that the diagnosis of hyposmia in COVID-19 patients was mainly made through subjective symptomatology collected by questionnaires and/or interview. Psychophysical tests were carried out in a few studies showing significant discrepancies between the self-reported sense of smell and test results. To date the methods used by authors to investigate smell impairment in COVID-19 patients have been very heterogeneous and predominantly based on self-reported questionnaires leading to confusing and inconclusive results. We suggest that simple validated self-administered psychophysical olfactory tests could be a valuable instrument to investigate isolated/quarantined or hospitalised COVID-19 patients referring smell impairment in order to confirm olfactory dysfunction.

KEY WORDS: hyposmia, COVID-19, SARS-CoV-2, olfaction, olfactory test, surveys

RIASSUNTO

Da dicembre 2019, in seguito alla comparsa in Cina di una nuova infezione da Coronavirus (COVID-19), si è assistito alla diffusione di una pandemia. In un numero significativo di pazienti è stata riscontrata la comparsa di alterazioni dell'olfatto anche in assenza di altri sintomi tipici dell'infezione. In questa revisione della letteratura sono stati inclusi gli articoli pubblicati da gennaio 2020 sull'alterazione olfattiva nei pazienti COVID-19 e in particolare i metodi utilizzati per la diagnosi. L'analisi della letteratura ha mostrato che la diagnosi dell'alterazione olfattiva in questi pazienti è stata eseguita principalmente mediante questionari. Pochi studi si sono basati sulla valutazione olfattiva mediante test psicofisici validati. Sono emerse discrepanze tra l'alterazione olfattiva riportata nei questionari e la valutazione olfattiva eseguita mediante test psicofisici. Ad oggi lo studio dell'olfatto nei pazienti COVID-19 è stato eseguito in maniera eterogenea e principalmente basata sui sintomi riferiti dai pazienti portando a risultati spesso contrastanti. Gli autori suggeriscono di utilizzare test olfattivi psicofisici, semplici, validati e somministrabili anche in assenza di un operatore al fine di confermare l'alterazione olfattiva in questi pazienti che spesso sono in quarantena, isolati o ospedalizzati.

PAROLE CHIAVE: *iposmia, anosmia, COVID-19, SARS-CoV-2, olfatto, test olfattivi, questionari*

Received: May 17, 2020
Accepted: June 19, 2020

Correspondence
Giancarlo Ottaviano
Department Neurosciences, Otolaryngology Section, University of Padova, via Giustiniani 2, 35100 Padua, Italy
Tel. +39 049 8214470. Fax +39 049 8213113
E-mail: giancarlo.ottaviano@unipd.it

Funding
None

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Marchese-Ragona R, Restivo DA, De Corso E, et al. Loss of smell in COVID-19 patients: a critical review with emphasis on the use of olfactory tests. Acta Otorhinolaryngol Ital 2020;40:241-247. https://doi.org/10.14639/0392-100X-N0862

Introduction

Since December 2019, a novel coronavirus SARS-CoV-2 (COVID-19) outbreak emerged in Wuhan, China, and subsequently rapidly spread to several countries [1].

The clinical manifestations of COVID-19 range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome. Guan et al. [2], in a comprehensive review of patients affected by SARS-CoV-2, described the clinical presentation of 7,736 patients who were hospitalised in China. Fever, the most frequent symptom, was present in 43.8% to 88.7% of cases. Other reported symptoms included cough (67.8%), fatigue (38.1%), sputum production (33.7%), shortness of breath (18.7%), myalgia or arthralgia (14.9%), sore throat (13.9%), headache (13.6%), chills (11.5%), nausea or vomiting (5%), diarrhoea (3.8%), nasal congestion (4.8%), haemoptysis (0.9%) and conjunctival congestion (0.8%). Alterations in taste or smell were not reported among the clinical symptoms. Mao et al. [3], studying 214 consecutive patients with laboratory-confirmed diagnosis of SARS-COV-2, reported in 36.4% both central and peripheral nervous system manifestations. Among the latter, hypogeusia and hyposmia were reported in 5.6 and 5.1% of cases, respectively. After this first report, numerous other cases of hyposmia in patients suffering from COVID-19 have been reported in the media and scientific journals, especially otolaryngology journals, so that a less serious variant of COVID-19 responsible for this symptomatology has been hypothesised [4]. Given these reports, the British Rhinological Society (BRS), as well as the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), recommended that the smell loss should be considered a marker of COVID-19 infection [5,6].

Herein, we critically reviewed reports about the methods used to date to quantify olfactory loss in COVID-19 patients, highlighting the limitations of subjective olfactory assessment and the importance of using validated olfactory tests during this pandemic.

Methodology of search strategy

We performed a full systematic review of the literature including English-language articles that were screened from several databases (PubMed, Medline, Web of Science and Google Scholar) and published from January 2020. Literature searches were performed in the beginning of May 2020. We searched articles using MeSH-terms, and/or text words such as "COVID-19", "SARS-CoV-2", "smell", "smell loss", "anosmia", "hyposmia" and "olfactory dysfunction". Titles were screened for relevance, followed by review of the abstract and full text. We only included peer-reviewed papers. This resulted in 24 papers that were discussed in this review. A total of 45 references were used in the full document. We did not include in this critical review articles reporting on 10 or less confirmed SARS-CoV-2 positive patients, unless a validated olfactory test was performed. Generally, we excluded articles with the lack of confirmed COVID-19 status. We divided the identified studies in two major groups, based on the methodology used to detect impairment of smell, and specifically studies using simple surveys or data extracted by medical records and studies using validated olfactory tests.

Sense of smell evaluation in confirmed COVID-19 patients by survey, questionnaires, or medical records

The majority of published studies concerning olfactory dysfunction in patients with COVID-19 infection have used survey questionnaires.

Hopkins et al. [5], of 2,428 subjects (most of them unconfirmed for COVID-19) who complained of smell loss, identified 74.4% reporting anosmia and 17.3% very severe smell loss. Interestingly, of the 80 patients who underwent nasopharyngeal swabs for COVID-19, only 74% tested positive for the virus.

Via telephone interview, Lee and co-workers [7] evaluated 3,191 laboratory confirmed COVID-19 patients complaining of acute anosmia or ageusia. Smell/taste loss was reported by 15.3% of patients (n = 488). Among these, only olfactory loss was reported by 27.7% of patients, ageusia by 20.3% and both by 52%. Similarly, Heidari et al., Clemency et al. and Gudbjartsson et al. evaluated their COVID-19 patients who complained of olfactory dysfunction through a telephone interview/verbal questionnaire [8-10]. A multicentre questionnaire study [11], based on 417 mild-moderate COVID-19 patients, reported olfactory dysfunction in 85.6% of cases (n = 357). Among these, 284 (79.6%) referred anosmia, while 73 (20.4%) hyposmia. Furthermore, phantosmia and parosmia affected 12.6% and 32.4% of patients, respectively. Olfactory dysfunction appeared before (11.8%), after (65.4%) or simultaneously (22.8%) to the appearance of general or ENT symptoms. According to the authors, 25.5% of patients recovered both their sense of smell and taste during the 2 weeks following resolution of general symptoms. Among the cured patients who had residual gustatory and/or olfactory dysfunction, 53.9% complained of isolated olfactory dysfunction, while 22.5% of isolated gustatory dysfunction and 23.6% of both. Females seemed to be more affected by smell and taste dysfunctions than males [11]. Leichien et al. [12] evaluated by questionnaire 1,420 mild-moderate COVID-19 positive patients. Anosmia

was one of most prevalent symptoms and was reported in about 70.2% of patients. Smell loss lasted at least 7 days after the disease in 37.5% of healed patients. Benezit et al. [13], evaluating 259 COVID-19 positive patients through a web-based questionnaire, found that 20% of the respondents complained of hyposmia, 24% of hypogeusia and 17% of both. Other authors have reported anosmia/hyposmia through surveys in COVID-19 positive patients. Among these, Kaye et al. [14] reported that 237 COVID-19 patients, using the AAO-HNS COVID-19 Anosmia Reporting Tool for clinicians [15], complained of anosmia. In particular, 73% reported anosmia before a diagnosis of COVID-19, while 27% after. Adding smell loss to a symptom tracker phone app, Menni et al. [16] obtained surveys from 7178 subjects who reported having been tested positive for COVID-19. Of these, 65.03% complained of smell/taste loss.

Some papers reported the results of case-control studies. Beltran-Corbellini et al. [17], studying 79 SARS-CoV2 positive patients and 40 controls (patients positive for influenza) by surveys, found that smell and taste complaints were significantly more frequent in cases than in controls. Furthermore, considering only the study group, they found that the patients complaining of smell/taste alterations were significantly younger than patients without these complaints. Similarly, studying 59 COVID patients and 203 controls (COVID-19 negative patients with influenza-like symptoms) Yan et al. [18] found that the referred smell/taste impairments was independently and strongly associated with COVID-19-positivity. Finally Wee et al. [19], studying 154 patients positive to COVID-19 and 71 patients tested positive for other respiratory viruses, found olfactory/taste dysfunction being self-reported by 22.7% of the patients of the former group and by only 2.8% of the patients of the latter. The authors concluded that self-reported olfactory dysfunction had high specificity as a screening criterion for COVID-19.

Studying retrospectively smell and taste data from 128 COVID-19 patients, Yan et al. [20] observed that only 26 (20.1%) required hospitalisation. Very interestingly, referred anosmia was found to be an independent factor for outpatient care. The authors concluded that smell loss in COVID-19 might be associated with a milder clinical course, as already hypothesised by Gane and coworkers [4] and Lee and co-workers [7]. This could be one of the reasons why hospitalised patients usually complain less of smell/taste dysfunction. Aggarwal et al. [21], evaluating 43 COVID-19 positive hospitalised patients (16 of whom hospitalised for the infection), observed that on surveys smell/taste loss was reported in a very low percentage of patients (19%). The mean population age was 65.5 and 75% were males. Giacomelli et al. [22] found that 33.9% of COVID-19 hospitalised patients reported on surveys either taste or olfactory alterations, while 18.6% reported both. Similar results, obtained mainly on hospitalised patients, were reported by Klopfenstein and coworkers who observed in surveys that 47% of their 114 COVID-19 patients reported olfactory alteration (anosmia) and about 85% (46 patients) also suffered of dysgeusia [23].

Some studies evaluated the reported sense of smell symptom together with patients reported outcome measures (PROMS), such as VAS (visual analogue scale) or SNOT 22 (sinonasal outcome test-22). Yan et al. [18] studied 59 COVID-19 patients and asked them to fill in a VAS for smell and taste. After showing that 40 patients (68%) reported smell and 42 (71%) gustatory impairment, the authors described a referred improvement of both senses with the clinical resolution of the infection in the majority of the patients. SNOT-22 has also been used in order to study the rhinological symptoms of 202 COVID-19 patients. In this study, 64% of the patients interviewed referred altered sense of smell/taste. At SNOT-22, among the patients complaining of olfactory dysfunction, 34% also complained nasal obstruction. Smell loss, as isolated symptoms, was reported by only 6 patients [24].

Sense of smell evaluation in confirmed COVID-19 patients by olfactory test

Few studies in the literature have adopted validated olfactory tests to confirm the olfactory loss reported by COVID-19 patients and to assess its severity.

Eliezer et al. [25] described the case of a 40-year-old woman, COVID-19 positive with acute hyposmia. A five-odour identification test confirmed the olfactory alteration, while CT scans and MRI of the nasal cavities showed bilateral inflammatory obstruction of the olfactory fissures without abnormalities of the bulbs and olfactory traits. Ottaviano et al. [26] studied 6 COVID-19 patients complaining of sudden hyposmia by the "Le Nez du Vin" test, a six-odours smell identification test and in all cases found an olfactory deficit. In a study by Lechien et al. [27], of 78 subjects complaining of isolated sudden hyposmia, 46 COVID-19 positive patients underwent the "Sniffin Sticks" identification sub-test (16 odours). The authors found that 52% of the patients were anosmic, 11 (24%) were hyposmic. It should be noted that 11 patients had normal olfaction (24%).

In a case-control study by Moein et al. [28], 60 patients with COVID-19 (not necessarily complaining of olfactory dysfunction) carried out an olfactory study using the Persian version of the University of Pennsylvania Smell Identification Test (UPSIT). Only 35% of COVID-19 patients were aware of their olfactory deficiency, while the

olfactory test showed that almost all patients (98%) had a measured olfactory dysfunction. According to UPSIT standards, 58% of patients were either severely hyposmic or anosmic, 27% had a moderate hyposmia, 13% a mild hyposmia and only one patient (2%) had normal sense of smell.

Vaira et al. [29] evaluated 72 COVID-19 patients using the Connecticut Chemosensory Clinical Research Center (CCCRC) test, finding that the majority of the patients (about 83%) were affected by smell dysfunction (either hyposmia or anosmia), although only 61% of patients reported having or having had olfactory loss. Of importance, 28 patients who no longer referred olfactory dysfunction at the time of the visit were found to be hyposmic at the smell test [29].

Discussion

Olfactory dysfunction can be either conductive, mainly caused by sinusitis and rhinitis due to the physical blockage of odours in reaching the receptors of olfactory neurons, or sensorineural, involving the interruption of the pathway between olfactory receptors and the olfactory cortex, mainly caused by viral infections, head injuries or neurodegenerative diseases (i.e.: Parkinson's and Alzheimer's diseases) [30-32].

In general, three different types of olfactory (no radiological) testing exist: subjective (patient reported) olfactory assessment, psychophysical olfactory assessment and olfactory assessment based on electrophysiological studies [31,33]. The method used for assessing olfactory dysfunction is extremely important for accurate diagnosis, reporting outcomes and tracking olfactory changes over time [31]. This should be considered even more important during an outbreak in which olfactory dysfunction seems to be one of the most frequently reported symptoms.

Validated questionnaires or recognised forms of evaluation, possibly quantitative and/or anchored, such as a VAS, can be used in the study of hyposmia. Nevertheless, self-assessment is not well related to the measured olfactory function [30,31,33], as it has been well shown in the few studies where olfactory tests have been performed in COVID-19 positive patients. In particular, Lechein et al. [27] found that 24% of COVID-19 patients complaining of olfactory loss were normal by the smell test, whereas Moein and colleagues [28] and Vaira et al. [29] observed an underestimation of the self-reported smell dysfunction. In this regard, it is known that in the general population only for anosmia is there correspondence between self-reported olfactory function and the measured one [31,33]. Due to this lack of precision, subjective evaluation of the sense of smell should always be associated with a validated olfactory test to determine the severity of the dysfunction. Furthermore, the measurement of the olfactory function with validated olfactory tests allow quantification of the extent of smell reduction and to evaluate it during clinical follow-up [31,33].

Psychophysical and electrophysiological procedures are the most effective approaches to assess the integrity of the olfactory system in humans. Electrophysiological tests, such as olfactory event-related potentials, give an objective measure of smell, but are complex and necessitate of expensive equipment, so their clinical use is limited and are mainly reserved for research purposes [30,32,33]. Psychophysical tests, in which subjects are requested to provide a volitional response to the presentation of odourant stimuli, are much more known. Being easy to use, these tests are the most widely employed for quantifying olfactory function in clinical practice [31,32,34].

Psychophysical olfactory tests can be divided into the threshold and supra-threshold tests. The olfactory threshold is the concentration of an odour in which 50% of stimuli are detected and 50% remain imperceptible to a subject. The supra-threshold olfactory test involves the presentation of the odour with stimuli of sufficient concentration so that they are detectable to the subject. Among commercially available psychophysical olfactory tests, the most widely known are the UPSIT and the Sniffin' Sticks. UPSIT is a standardised microencapsulated odourant identification test where 40 odourants are presented in a scratch and sniff format with 4 response alternatives accompanying each odour, able to identify normosmia, mild, medium, severe hyposmia and anosmia. Sniffin' Sticks uses reusable pen-like odour dispensing devices that are presented to the subject by an examiner and consists of three subtests, which allow the study of odour threshold (for n-butanol/phenyl ethyl alcohol), discrimination of 16 odourant triplets and identification of 16 odours. The latter subtest is performed using a multiple-choice task (identification of individual odours is performed from lists of four descriptors for each odour). The sum of the 3 subtest results gives a composite score, known as TDI, which can indicate normal olfactory function, hyposmia, or anosmia [30-33,35,36]. CCCRC is also a composite test, being based on threshold for n-butanol and identification of 10 odour subtests [32]. Some shortened psychophysical olfactory tests are also available, mainly based on odour identification [31-33,37]. The number of items presented can range from 4 (4-Item Pocket Smell Test) to 12 odours [Screening 12 test, Cross-Cultural Smell Identification Test (CC-SIT)] [32,33,37]. When based on a small number of odours (up to 12), smell identification tests are mainly considered screening olfactory tests. Nevertheless, the use of these psychophysical instruments should be considered preferable to subjective assessment

alone, as questionnaires on self-represented symptoms are not as sensitive or specific as odour identification tests, particularly for mild hyposmia [31-33].

Viral infections of the upper respiratory tract are the most common cause of hyposmia or permanent anosmia. This loss of smell can reflect damage not only to the olfactory epithelium, but also to central olfactory structures following a viral invasion into the brain. Suzuki et al. [38] identified coronavirus in nasal secretions in a patient with post-viral olfactory dysfunction. The potential route of entry into the central nervous system of SARS-CoV-2 has not yet been established, but several mechanisms including invasion of olfactory nerves and retrograde invasion of the CNS, haematogenous or lymphatic routes all seem to be possible [39]. The movement of the COVID-19 virus to the brain via the cribriform plate close to the olfactory bulb has been proposed as possible route for the virus to reach the brain [40]. An olfactory cleft disease has also been hypothesised as a cause of olfactory loss in patients with COVID-19 [25]. Interestingly, very recently, neurobiologists from Harvard Medical School analysed bulk and single-cell RNA-Seq datasets to identify cell types in the olfactory epithelium that express molecules that mediate infection by SARS-CoV-2. They found in both mouse and human datasets that olfactory sensory neurons do not express two key genes required for CoV-2 entry, ACE2 and TMPRSS2. In contrast, non-neural cells in the olfactory epithelium, olfactory epithelial support cells and stem cells of olfactory epithelium express both of these genes, suggesting that infection of these cells could directly or indirectly lead to olfactory dysfunction [41].

Conclusions

The human sense of smell can be evaluated through subjective methods and/or either psychophysical or electrophysiological olfactory tests. To date, the methods

Table I. Screening and olfactory testing methods used in COVID-19 positive patients.

	Patients complaining of or with smell alterations	Verbal questionnaire	Online questionnaire	Telephone interview	Smart-phone app	UPSIT	Sniffin' sticks	Nez du vin	Simple odourants	CCCRC	PROMS
Mao [3]	11	X									
Hopkins [5]	2,428#		X								
Lee [7]	389			X							
Lechien [11]	357	X									
Lechien [12]	997	X		X##							
Bénézit [13]	95		X								
Kaye [14]	237		X								
Menni [16]	4,668				X*						
Beltrán-Corbellini [17]	25	X									
Yan [18]	40		X								X
Wee [19]	35	X									
Yan [20]	75	X°	X°	X°							
Giacomelli [22]	31	X									
Klopfenstein [23]	54	X									
Spinato [24]	130			X							X
Eliezer [25]	1								X^		
Ottaviano [26]	6							X§			X
Lechien [27]	78	X					X^^				
Moein [28]	59					X**					
Vaira [29]	72	X***								X	
Heidari [8]	23	X									
Clemency [9]	110			X							
Gudbjartsson [10]	119°°			X							

** COVID-19 symptom tracking. Android and IOS app; ** Persian version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT); *** Not clear if questionnaire or telephone interview; ^ Smell test with 5 odourants: flower rose, caramel, goat cheese, fruits, manure; ^^ Sniffin sticks 16 odours identification sub-test only in 46; § Identification test (6 odours); # Lack of confirmed COVID-19 status in most of the cases; ## In cases of patient isolation; ° Data obtained by electronic medical records. If data were not available, patients were either emailed or called; °° Loss of smell and taste were reported together.*

used to investigate smell impairment in COVID-19 patients have been very heterogeneous (Tab. I). Most of the publications that we identified in this review are based on olfactory self-assessment that is unreliable in COVID-19 patients compared to psychophysical tests [27-29,42], especially in the context of a pandemic scenario and consequent restrictions in social life [43]. The authors probably opted for self-administered questionnaire because it can be very difficult to perform an olfactory test during SARS-CoV-2 outbreak, especially when testing recently infected patients. In fact, these patients are isolated or hospitalised, some olfactory tests require an operator who can alter the test result with the protective suit, while other tests are not disposable. For all these reasons, the results of the available studies are not conclusive and many questions remain unanswered about the actual incidence of smell impairment during COVID- 19 infection, its predictive value of a mild- moderate severity of the disease and the percentage of patients recovering.

Given to their simplicity, psychophysical tests, in which the subjects are requested to provide a volitional response to the presentation of odourant stimuli, are the most widely employed for quantifying olfactory dysfunction. Among these, odour identification tests are the most simple and fast [32]. It would also be important to use disposable tests, since SARS-CoV-2 can remain viable on plastic, stainless steel and cardboard for up to 72 hours [44]. Although home-quarantined/isolated COVID-19 patients were able to perform the CCCRC in a self-administered way [45], the UPSIT, being self-administered and readily available, should be preferred. Other shorter validated psychophysical tests, such as the CC-SIT (12 odours), the smell Diskettes Test (8 odours) and "Le Nez du Vin" (6 odours), being disposable and not requiring the supervision of a physician/nurse, could also be proposed to test patients in quarantine/isolation and possibly still contagious patients.

The involvement of taste in COVID-19 patients with chemosensory symptoms could be most probably secondary to smell loss [30,31]. Based on gustatory screening test, some authors found that 47% of patients studied with COVID-19 had taste changes [29]. To confirm these data, full gustatory testing, i.e. using taste strips [31], should be performed to confirm and quantify the taste dysfunction in COVID-19 patients.

In March 2020, the AAOHNS and BRS proposed that hyposmia and dysgeusia (in the absence of other respiratory diseases) should be added to the symptoms used to screen for CoV-2 infection [5,6]. We suggest that validated psychophysical self-administered tests could be valuable methods to investigate smell impairment in COVID-19 patients to identify as accurately as possible cases needing of closer post-infection follow-up.

More extensive studies based on validated psychophysical olfactory tests (systematically performed during active infection) may help to assess the frequency of hyposmia among COVID-19 patients, its pathogenesis, duration and potential role as a marker of disease progression or severity.

References

1 Johns Hopkins Center for Systems Science and Engineering 2019-nCoV global cases. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

2 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20. https://doi.org/10.1056/NEJMoa2002032

3 Mao L, Jin H, Wang M, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. JAMA Neurol 2020;77:1-9. https://doi.org/10.1001/jamaneurol.2020.1127

4 Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? Rhinology 2020;58:299-301. https://doi.org/10.4193/Rhin20.114

5 Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. Rhinology 2020;58:295-8 https://doi.org/10.4193/Rhin20.116

6 Lechien JR, Hopkins C, Saussez S. Sniffing out the evidence; it's now time for public health bodies recognize the link between COVID-19 and smell and taste disturbance. Rhinology 2020;58:402-3. https://doi.org/10.4193/Rhin20.159

7 Lee Y, Min P, Lee S, et al. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020;35:e174. https://doi.org/10.3346/jkms.2020.35.e174

8 Heidari F, Karimi E, Firouzifar M, et al. Anosmia as a prominent-symptom of COVID-19 infection. Rhinology 2020;58:302-3. https://doi.org/10.4193/Rhin20.140

9 Clemency BM, Varughese R, Scheafer DK, et sl. Symptom criteria for COVID-19 testing of heath care workers. Acad Emerg Med 2020;27:469-74. https://doi.org/10.1111/acem.14009

10 Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARSCoV-2 in the Icelandic population. N Engl J Med 2020;382:2302-15. https://doi.org/10.1056/NEJMoa2006100

11 Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter european study. Eur Arch Otorhinolaryngol 2020;277:2251-61. https://doi.org/10.1007/s00405-020-05965-1

12 Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1,420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med 2020;288:335-44. https://doi.org/10.1111/joim.13089

13 Bénézit F, Le Turnier P, Declerck C, et al. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. Lancet Infect Dis 2020;20:1014-5. https://doi.org/10.1016/S1473-3099(20)30297-8

14 Kaye R, Chang CWD, Kazahaya K, et al. COVID-19 anosmia reporting tool: initial findings. Otolaryngol Head Neck Surg 2020;163:132-4. https://doi.org/10.1177/0194599820922992

15 American Academy of Otolaryngology-Head and Neck Surgery. COVID-19 anosmia reporting tool for clinicians. https://www.entnet.org/content/new-covid-19-anosmia-reporting-tool. March 26, 2020.

16 Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of

self-reported symptoms to predict potential COVID-19. Nat Med 2020;26:1037-40. https://doi.org/10.1038/s41591-020-0916-2

17 Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of Covid-19: a pilot multicenter PCR-based case-control study. Eur J Neurol 2020;27:1738-41. https://doi.org/10.1111/ene.14273

18 Yan CH, Faraji F, Prajapati DP, et al. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 2020;10:806-13. https://doi.org/10.1002/alr.22579

19 Wee LE, Chan YFZ, Teo NWY, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected COVID-19. Eur Arch Otorhinolaryngol 2020;277:2389-90. https://doi.org/10.1007/s00405-020-05999-5

20 Yan CH, Faraji F, Prajapati DP, et al. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. Int Forum Allergy Rhinol 2020;10:821-31. https://doi.org/10.1002/alr.22592

21 Aggarwal S, Garcia-Telles N, Aggarwal G, et al. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. Diagnosis (Berl) 2020;7:91-6. https://doi.org/10.1515/dx-2020-0046

22 Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis 2020;71:889-90. https://doi.org/10.1093/cid/ciaa330

23 Klopfenstein T, Kadiane-Oussou NJ, Toko L, et al. Features of anosmia in COVID-19. Med Mal Infect 2020;50:436-9. https://doi.org/10.1016/j.medmal.2020.04.006

24 Spinato G, Fabbris C, Polesel J, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA 2020;323:2089-90. https://doi.org/10.1001/jama.2020.6771

25 Eliezer M, Hautefort C, Hamel AL, et al. Sudden and complete olfactory loss function as a possible symptom of COVID-19. JAMA Otolaryngol Head Neck Surg 2020;146:674-5. https://doi.org/10.1001/jamaoto.2020.0832

26 Ottaviano G, Carecchio M, Scarpa B, et al. Olfactory and rhinological evaluations in SARS-CoV-2 patients complaining of olfactory loss. Rhinology 2020;58:400-1. https://doi.org/10.4193/Rhin20.136

27 Lechien JR, Cabaraux P, Chiesa-Estomba CM, et al. Psychophysical olfactory tests and detection of COVID-19 in patients with sudden onset olfactory dysfunction: a prospective study Ear Nose Throat J 2020 May 29:145561320929169 [online ahead of print]. https://doi.org/10.1177/0145561320929169

28 Moein ST, Hashemian SMR, Mansourafshar B, et al. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol 2020;10:944-50. https://doi.org/10.1002/alr.22587

29 Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. Head Neck 2020;42:1252-8. https://doi.org/10.1002/hed.26204

30 Doty RL. The olfactory system and its disorders. Semin Neurol 2009;29:74-81. https://doi.org/10.1002/hed.26204

31 Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. Rhinol Suppl 2017;54:1-30. https://doi.org/10.4193/Rhino16.248

32 Ottaviano G, Frasson G, Nardello E, et al. Olfaction deterioration in cognitive disorders in the elderly. Aging Clin Exp Res 2016;28:37-45. https://doi.org/10.1007/s40520-015-0380-x

33 Rimmer J, Hellings P, Lund VJ, et al. European position paper on diagnostic tools in rhinology. Rhinology 2019;57(Suppl 28):1-41. https://doi.org/10.4193/Rhin19.410

34 Marioni G, Ottaviano G, Staffieri A, et al. Nasal functional modifications after physical exercise: olfactory threshold and peak nasal inspiratory flow. Rhinology 2010;48:277-80. https://doi.org/10.4193/Rhin09.141

35 Gelardi M, Piccininni K, Quaranta N, et al. Olfactory dysfunction in patients with chronic rhinosinusitis with nasal polyps is associated with clinical-cytological grading severity. Acta Otorhinolaryngol Ital 2019;39:329-35. https://doi.org/10.14639/0392-100X-2426

36 Magliulo G, De Vincentiis M, Iannella G, et al. Olfactory evaluation in obstructive sleep apnoea patients. Acta Otorhinolaryngol Ital 2018;38:338-45. https://doi.org/10.14639/0392-100X-1981

37 McMahon C, Scadding GK. Le Nez du Vin - a quick test of olfaction. Clin Otolaryngol Allied Sci 1996;2:278-80. https://doi.org/10.1111/j.1365-2273.1996.tb01741.x

38 Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 2007;117:272-7. https://doi.org/10.1097/01.mlg.0000249922.37381.1e

39 Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020;92:552-5. https://doi.org/10.1002/jmv.25728

40 Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020;11:995-8. https://doi.org/10.1021/acschemneuro.0c00122

41 Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020;6:eabc5801. https://doi.org/10.1126/sciadv.abc5801

42 Soler ZM, Patel ZM, Turner JH, et al. A primer on viral-associated olfactory loss in the era of COVID-19. Int Forum Allergy Rhinol 2020;10:814-20. https://doi.org/10.1002/alr.22578.

43 Passali GC, Bentivoglio AR. Comment to the article "Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study". Eur Arch Otorhinolaryngol 2020;277:2391-2. https://doi 10.1007/s00405-020-06024-5

44 Van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020;382:1564-7. https://doi.org/10.1056/NEJMc2004973

45 Vaira LA, Salzano G, Petrocelli M, et al. Validation of a self-administered olfactory and gustatory test for the remotely evaluation of COVID-19 patients in home quarantine. Head Neck 2020;42:1570-6. https://doi.org/10.1002/hed.26228