The Smell in COVID-19 Infection: Diagnostic Opportunities

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ABSTRACT There is a high prevalence of olfaction changes, especially in the early presentation, in coronavirus disease-19 (COVID-19) patients. The mechanisms through which the virus leads to anosmia/hyposmia are still not fully understood. However, olfaction changes could be used as an indication for testing or quarantine. Screening for infections and other diseases by recognizing volatile organic compounds (VOCs) has been previously conducted. Hence, if the coronavirus infection also results in VOCs excretion, physicians could "smell" the virus by using electronic noses. We conducted a literature review on olfaction changes and the COVID-19. Our results suggest that these changes could be used as an indication for early testing, even as an isolated symptom. We propose that the electronic nose could be used as a future screening tool, especially in agglomeration spaces such as airports, for screening for the COVID-19 infection.

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KEY WORDS: coronavirus disease-2019 (COVID-19), electronic nose, olfaction, smell

The olfaction in COVID-19

The coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an infectious condition that rapidly spread internationally. It was defined as a pandemic in March 2020 by the World Health Organisation. Health systems worldwide were alarmed. It has been described as a large spectrum of symptoms from asymptomatic to severe systemic disease. Its classic symptoms include fever, fatigue, dry cough, myalgia, and dyspnea [1,2]. The confirmation of the disease has been performed by real-time reverse-transcription polymerase chain (rt-PCR) identification of the viral RNA and serological assays to SARS-CoV-2, the last mainly being used in asymptomatic population to map and prevent the spread [3].

Evidence shows that anosmia/hyposmia is a common symptom in the early phase of COVID-19 infection, commonly also seen as the only clinical manifestation in positive-tested patients

Although anosmia and olfactory alterations are still not officially recognized as one of the COVID-19 symptoms, it has been widely reported as a common initial finding in patients tested positive for the virus infection [4-8]. Moreover, it has also been reported in patients who presented with no other respiratory symptoms [9]. An Italian study showed that from 202 COVID-19 patients, almost 25% presented with olfactory alterations as the only symptom or prior to others [10]. In addition, during the COVID-19 pandemic, a study in London described the new onset of anosmia in 2428 patients: 17% had no other symptoms and 51% had at least one symptom that pointed to self-isolation, such as fever or cough [11]. In another study in the United States, 73% of 237 COVID-19 confirmed patients presented with anosmia prior to the diagnosis and almost 27% presented with it as the initial symptom [6]. At the University of Pennsylvania, USA, a quantitative smell testing was applied to 60 confirmed COVID-19 patients and to 60 controls matched for gender and age. Results showed that COVID-19 infected patients had a higher incidence, with 98% having a level of olfactory dysfunction and more than half being either completely anosmic or with severe hyposmia [12].

The exact mechanism through which SARS-Cov-2 interferes in the sense of smell raised curiosity in the scientific community, but it is still unclear [13]. The cellular receptor for the virus, angiotensin-converting enzyme 2 (ACE2), is largely found in the nasal mucosa and known to have a role in respiratory inflammation regulation, such as its influence in bradykinin levels [14,15]. Nonetheless, the olfactory alterations found in COVID-19 patients most commonly are not associated with rhinitis symptoms [4,5]. Thus, one theory is that SARS-CoV-2 leads to those symptoms by causing damage in the olfactory pathways instead of local inflammation and congestion. Anosmia was also a symptom in other coronavirus infections [16]. When analyzing the effects of SARS-CoV-1 in the central nervous system, a study performed in transgenic mice for the human ACE2 receptor did not detect signs of local inflammation and suggested that there was a neuronal death secondary to a

cytokines storm, specially IL-6, that followed the viral stimulation in the mice [17].

The COVID-19 olfactory disruption has been reported to regain function a few weeks after its onset and, moreover, the neurologic symptoms are significantly less common than the olfactory ones, not corroborating with the neuronal definitive damage hypothesis [4-6,18,19]. Other non-neural ACE2 expressing cells found in the olfactory pathways were suggested to be responsible for the changes in those neurons function, including olfactory epithelium sustentacular cells, microvillar cells, Bowman's gland cells, horizontal basal cells, and olfactory bulb pericytes [20]. Those cells express two genes required for the SARS-CoV-2 entry, in contrast to olfactory sensory neurons [20]. Olfactory changes secondary to trauma or respiratory tract infection can commonly be demonstrated on olfactory bulb MRI as a reduction of volume of the olfactory bulb and its tract [21]. However, one recent report did not demonstrate those findings in a COVID-19 patient with anosmia [22].

Olfaction changes should be an indication for testing, for quarantine and possibly for early treatment in the future

Furthermore, olfactory changes were already associated with other immune responses involving cytokines, such as in autoimmune diseases [2,23-25]. Recently, COVID-19 has been described in correlation with autoimmune conditions, for example, with Guillain-Barre syndrome, anti-phospholipid syndrome, and Kawasaki disease [26-28]. Thus, there is a possibility that one of the mechanisms through which COVID-19 causes anosmia is related to autoimmunity.

Volatile organic compounds from excretions of infected individuals might be used to screen for COVID-19 infection by electronic noses in agglomeration spaces such as airports, malls, and conference venues

Smelling the coronavirus

Interestingly, smell could be related to COVID-19 infection screening in a reverse way, by potentially using an electronic nose to diagnose the infection in early stages. Many diseases generate volatile organic compounds (VOCs) in human excretions. For example, dogs were shown to be able to recognize specific VOCs from human urine, feces, and blood and to distinguish the samples from sick patients in diseases like prostate and lung cancer [29-32]. Electronic noses, devices that are able to identify VOCs, largely explored in the army and food industry, have been recently tried as a diagnostic innovation to systemic and infectious diseases, including various types of cancer [33,34]. The technology has already successfully identified in vitro infectious respiratory disease pathogens, such as *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Pseudomonas aeruginosa* [35,36]. Likewise, it has also shown to work in vivo with respiratory diseases, including aspergillosis, ventilator-associated pneumonia, pneumonia in COPD patients during exacerbation, and idiopathic pulmonary fibrosis [33,37-39]. Recently the Penn Vet-University of Pennsylvania website (https://www.vet.upenn.edu/about/press-room/press-releases/article/penn-vet-launches-covid-19-canine-scent-detection-study) published information about an on-going study in which odor imprinting techniques, commonly used to train dogs, were used to train Labrador retrievers to recognize VOCs in COVID-19 patients. This training would enable canine surveillance for screening the disease. There are still no published studies on electronic nose and COVID-19. However, if the dogs will be able to recognize it, VOCs released by COVID-19 patients could be a potential target for new screening and diagnostic tools, such as the electronic nose.

Conclusions

COVID-19 infection has been described as three main syndromes: asymptomatic, mild upper respiratory tract infection, and severe systemic disease. Most recently, it has been suggested that isolated onset of anosmia should be considered as a forth common syndrome of COVID-19 infection [8]. It is still not known exactly why SARS-CoV-2 leads to olfactory changes but there is evidence that this correlation exists. In addition, many other respiratory infectious diseases were shown to be successfully recognized by electronic devices that identify specific VOCs [37,40]. Therefore, we suggest that changes in olfaction during the pandemic should be considered as a critical sign for early identification of possibly infected individuals who should be tested and considered for early treatment and/or quarantine. In addition, using electronic noses to detect VOCs could be a potential target for new screening tests for COVID-19, and would be especially useful in agglomerations spots like airports, malls, and scientific conference venues.

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References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of

72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323 (13): 1239-42.

2. Shoenfeld Y. Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. *Autoimmun Rev* 2020; 19 (6): 102538.
3. Infantino M, Damiani A, Gobbi FL, et al. Serological assays for SARS-CoV-2 infectious disease: benefits, limitations and perspectives. *IMAJ* 2020; 22 (4): 203-10.
4. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. *Laryngoscope* 2020; 130 (7): 1787.
5. 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; 1-11.
6. Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny JC 3rd. COVID-19 anosmia reporting tool: initial findings. *Otolaryngol Head Neck Surg* 2020; 163 (1): 132-4.
7. Gilani S, Roditi R, Naraghi M. COVID-19 and anosmia in Tehran, Iran. *Med Hypotheses* 2020; 141: 109757.
8. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome?. *Rhinology* 2020; 58 (3): 299-301.
9. Lorenzo Villalba N, Maouche Y, Alonso Ortiz MB, et al. Anosmia and dysgeusia in the absence of other respiratory diseases: should COVID-19 infection be considered?. *Eur J Case Rep Intern Med* 2020; 7 (4): 001641.
10. 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 (20): 2089-90.
11. Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. *Rhinology* 2020; 58 (3): 295-8.
12. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol* 2020; 10.1002/alr.22587.
13. Vaira LA, Salzano G, Fois AG, Piombino P, De Riu G. Potential pathogenesis of ageusia and anosmia in COVID-19 patients. *Int Forum Allergy Rhinol* 2020; 10.1002/alr.22593.
14. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579 (7798): 270-3.
15. Ohkubo K, Lee CH, Baraniuk JN, Merida M, Hausfeld JN, Kaliner MA. Angiotensin-converting enzyme in the human nasal mucosa. *Am J Respir Cell Mol Biol* 1994; 11 (2): 173-80.
16. de Haro-Licer J, Roura-Moreno J, Vizitiu A, González-Fernández A, González-Ares JA. Long term serious olfactory loss in colds and/or flu. *Acta Otorrinolaringol Esp* 2013; 64 (5): 331-8.
17. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 2008; 82 (15): 7264-75.
18. Klopfenstein T, Kadiane-Oussou NJ, Toko L, et al. Features of anosmia in COVID-19 [published online ahead of print, 2020 Apr 17]. *Med Mal Infect* 2020; S0399-077X(20)30110-4.
19. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China [published online ahead of print, 2020 Apr 10]. *JAMA Neurol* 2020; 77 (6): 1-9.
20. Brann D, Tsukahara T, Weinreb C, Logan D Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. *bioRxiv* 2020 [Available from https://www.biorxiv.org/content/10.1101/2020.03.25.009084v3].
21. Pattisapu P, Lambert EM. Clinical image: olfactory bulb and tract aplasia/hypoplasia on MRI. *Otolaryngol Res Rev* 2017; 1 (1): 34-5.
22. Galougahi MK, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. Olfactory bulb magnetic resonance imaging in SARS-CoV-2-induced anosmia: the first report. *Acad Radiol* 2020; 27 (6): 892-3.
23. Perricone C, Shoenfeld N, Agmon-Levin N, de Carolis C, Perricone R, Shoenfeld Y. Smell and autoimmunity: a comprehensive review. *Clin Rev Allergy Immunol* 2013; 45 (1): 87-96.
24. Rattazzi L, Cariboni A, Poojara R, Shoenfeld Y, D'Acquisto F. Impaired sense of smell and altered olfactory system in RAG-1(-/-) immunodeficient mice. *Front Neurosci* 2015; 9: 318.
25. Katzav A, Ben-Ziv T, Blank M, Pick CG, Shoenfeld Y, Chapman J. Antibody-specific behavioral effects: intracerebroventricular injection of antiphospholipid antibodies induces hyperactive behavior while anti-ribosomal-P antibodies induces depression and smell deficits in mice. *J Neuroimmunol* 2014; 272 (1-2): 10-15.
26. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr* 2020; 10 (6): 537-40.
27. Alberti P, Beretta S, Piatti M, et al. Guillain-Barré syndrome related to COVID-19 infection. *Neurol Neuroimmunol Neuroinflamm* 2020; 7 (4): e741.
28. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. *N Engl J Med* 2020; 382 (17): e38.
29. Gao Q, Su X, Annabi MH, et al. Application of urinary volatile organic compounds (VOCs) for the diagnosis of prostate cancer. *Clin Genitourin Cancer* 2019; 17 (3): 183-90.
30. Mazzola SM, Pirrone F, Sedda G, et al. Two-step investigation of lung cancer detection by sniffer dogs. *J Breath Res* 2020; 14 (2): 026011.
31. Lippi G, Heaney LM. The "olfactory fingerprint": can diagnostics be improved by combining canine and digital noses?. *Clin Chem Lab Med* 2020; 58 (6): 958-67.
32. Cambau E, Poljak M. Sniffing animals as a diagnostic tool in infectious diseases. *Clin Microbiol Infect* 2020; 26 (4): 431-5.
33. Dragonieri S, Scioscia G, Quaranta VN, et al. Exhaled volatile organic compounds analysis by e-nose can detect idiopathic pulmonary fibrosis. *J Breath Res* 2020; 10.1088/1752-7163/ab8c2e.
34. Matsumoto K, Murakami Y, Shimizu Y, Hirayama T, Ishikawa W, Iwamura M. Electronic nose to distinguish bladder cancer by urinary odour feature: a pilot study. *Cancer Biomark* 2020; 28 (1): 33-9.
35. Lai SY, Deffenderfer OF, Hanson W, Phillips MP, Thaler ER. Identification of upper respiratory bacterial pathogens with the electronic nose. *Laryngoscope* 2002; 112 (6): 975-9.
36. Pavlou A, Turner APF, Magan N. Recognition of anaerobic bacterial isolates in vitro using electronic nose technology. *Lett Appl Microbiol* 2002; 35 (5): 366-9.
37. de Heer K, Kok MGM, Fens N, et al. Detection of airway colonization by aspergillus fumigatus by use of electronic nose technology in patients with cystic fibrosis. *J Clin Microbiol* 2016; 54 (3): 569-75.
38. Schnabel RM, Boumans MLL, Smolinska A, et al. Electronic nose analysis of exhaled breath to diagnose ventilator-associated pneumonia. *Respir Med* 2015; 109 (11): 1454-9.
39. Shafiek H, Fiorentino F, Merino JL, et al. Using the electronic nose to identify airway infection during COPD exacerbations. *PLoS One* 2015; 10 (9): e0135199.
40. Dragonieri S, Pennazza G, Carratu P, Resta O. Electronic nose technology in respiratory diseases. *Lung* 2017; 195 (2): 157-65.

"Transport of the mails, transport of the human voice, transport of flickering pictures - in this century, as in others, our highest accomplishments still have the single aim of bringing men together"

Antoine de Saint-Exupery (190–1944), best remembered for his novella The Little Prince (Le Petit Prince) and for his lyrical aviation writings, including Wind, Sand and Stars and Night Flight

Freedom is not worth having if it does not include the freedom to make mistakes.

Mahatma Gandhi (1869–1948), Indian political and spiritual leader