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Case report

Hypogeusia as the initial presenting symptom of COVID-19

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SUMMARY

COVID-19 is the disease caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first arose in Wuhan, China, in December 2019 and has since been declared a pandemic. The clinical sequelae vary from mild, self-limiting upper respiratory infection symptoms to severe respiratory distress, acute cardiopulmonary arrest and death. Otolaryngologists around the globe have reported a significant number of mild or otherwise asymptomatic patients with COVID-19 presenting with olfactory dysfunction. We present a case of COVID-19 resulting in intensive care unit (ICU) admission, presenting with the initial symptom of disrupted taste and flavour perception prior to respiratory involvement. After 4 days in the ICU and 6 days on the general medicine floor, our patient regained a majority of her sense of smell and was discharged with only lingering dysgeusia. In this paper, we review existing literature and the clinical course of SARS-CoV-2 in relation to the reported symptoms of hyposmia, hypogeusia and dysgeusia.

BACKGROUND

For many sick people with viral upper respiratory infections (URIs), the experience of eating food and perceiving flavour is often blunted either secondarily from rhinitis and resulting nasal obstruction or from direct viral injury to olfactory neuroepithelium. Retronasal olfaction, a combination of orthonasal smell and taste, is a sensory process that allows humans to perceive flavour, which is defined as the perception of anything beyond the five taste dimensions of food: sweet, salty, bitter, sour and umami.¹ This process is temporarily impaired during URIs due to mucosal inflammation and congestion of the nasal passages, thus physically blocking the entry of odour and flavour molecules to the olfactory cleft.² In contrast, post-URI olfactory loss is a neural process that occurs due to viral insult² and most commonly results in hyposmia late in the course of viral infection.³ This type of viral insult can result in either temporary loss of olfaction or, in some cases, permanent loss of smell.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of many pandemic coronaviruses that have been identified. The current outbreak of COVID-19 that began in Wuhan, China, has constituted a public health emergency of international concern, now creating a global impact with over 2.4 million cases to date.⁴ The clinical sequelae vary from mild and self-limiting URI symptoms to

severe respiratory distress, acute cardiopulmonary arrest and death.⁵ Coronaviruses have previously been identified as a family of viruses associated with anosmia.⁶ Anecdotal evidence from otolaryngologists worldwide has suggested that otherwise mild cases of COVID-19 caused by the novel betacoronavirus, SARS-CoV-2, may be significantly associated with olfactory dysfunction.

We present a case of COVID-19 resulting in ICU admission, presenting with the initial symptom of disrupted taste and flavour perception prior to respiratory involvement. The purpose of this paper was to review the clinical course of SARS-CoV-2 in relation to the reported symptom of hyposmia and hypogeusia.

CASE PRESENTATION

A 59-year-old African-American female presented to our institution by ambulance on 29 March 2020, secondary to several days of shortness of breath, fatigue and loss of appetite. Medical history was significant for hypertension, hyperlipidaemia and asthma, requiring infrequent use of albuterol reported less than one time per month. Social history was notable only for a remote history of tobacco abuse, but she denied any current tobacco, drug or alcohol use. Of note, the patient did endorse that her husband, whom she lives with at home, was complaining of shortness of breath and a non-productive cough several days prior to her arrival. Her husband's symptoms lasted only 3–4 days and had resolved completely. She reported no past otolaryngological surgeries or use of any nasal sprays, or homeopathic or herbal medications.

Roughly a week prior to admission, the patient began to experience a subtle decrease in appetite and disinterest in food. These symptoms were isolated and preceded any indication that she was ill. Over the week prior to her presentation, the foods she normally enjoys tasted 'bland and metallic'. The patient described her diet as 'varied and including many spices and strong flavours, particularly using herbs in Jamaican and Caribbean cuisines'. When questioned further, she also admitted to a slowly diminishing ability to smell that progressed to complete anosmia in the absence of congestion or any other nasal symptoms. However, she did not make the connection to this early symptom and the subsequent respiratory distress until specifically questioned. She noted in particular that when preparing her normal meals, she could no longer appreciate any of the typical culinary aromas.



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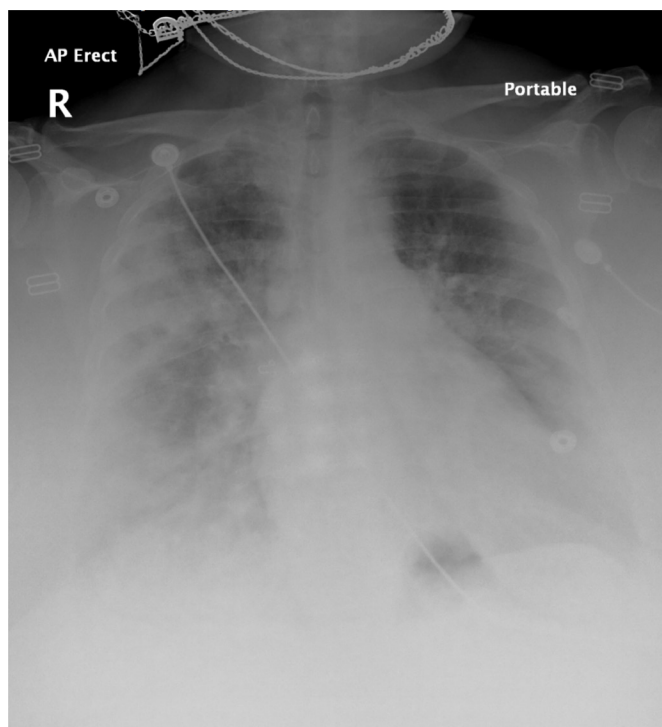


Figure 1 Chest radiograph, AP, day of admission. AP, anterior–posterior; R, right.

Further, she could not smell any of her scented candles but did not think anything of it at that time. The patient denied any history of hyposmia or anosmia prior to this. It was not until a few days later when she developed a non-productive cough, malaise, shortness of breath and chest tightness that ultimately prompted her to call 911. On transit to the hospital via ambulance, the patient had an initial SpO₂ of 68% on room air, and she was later placed on supplemental oxygen.

Review of symptoms was negative for any nasal obstruction, rhinorrhea, epistaxis, and nasal or head trauma. She endorsed shortness of breath, malaise and chest tightness as mentioned previously. On admission, the patient was afebrile and saturating adequately on 5 L supplemental oxygen via nasal cannula. The patient appeared fatigued and mildly distressed, and physical exam was notable for bilateral wheezes and rales, most predominant at the lung bases bilaterally. The patient had no appreciated mucosal or turbinate hypertrophy in the nasal cavity and otherwise had a normal head, eyes, ears, nose and throat examination.

INVESTIGATIONS

Laboratory values were significant for lactate dehydrogenase (410), erythrocyte sedimentation rate (42) and C reactive protein (192.1). Basic metabolic panel, liver function, renal function, myocardial enzymes and serum procalcitonin were otherwise normal. Tests for influenza A/B and *Legionella* were negative. A SARS-CoV-2 nucleic acid amplification test (NAAT) was taken by nasopharyngeal swab. A chest radiograph (see figure 1) followed by a high-resolution CT of the chest were performed, images of which reported multiple patchy ground-glass opacities in bilateral subpleural areas (see figure 2).

TREATMENT

Based on the overall clinical picture, the patient remained on contact and droplet precautions and isolation as it was assumed that she did have COVID-19. On the consult of our infectious

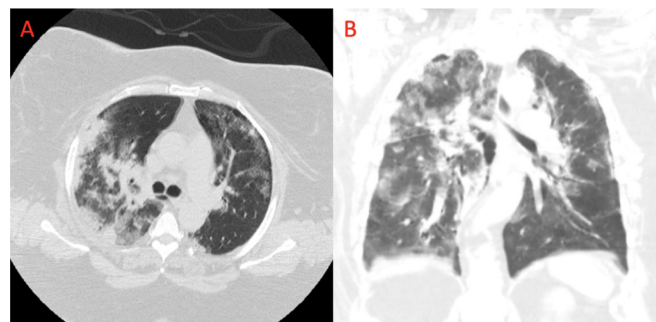


Figure 2 Chest CT, axial (A) and coronal (B), day of admission.

disease physician and checking the patient's corrected QT interval (QTc), the patient was empirically treated with the experimental therapy of hydroxychloroquine 400 mg two times per day for 1 day followed by 200 mg two times per day for 4 days, as well as azithromycin 500 mg two times per day for 1 day followed by 250 mg two times per day for 4 days.

The patient was subsequently transferred from the general floor to the ICU on the night of admission due to increased oxygen requirements with significant desaturations. The patient was initially placed on a non-rebreather and transitioned to continuous positive airway pressure (CPAP). On the advice of our pulmonologist, she remained on CPAP and intravenous steroids were initiated. The decision of early and pre-emptive intubation was discussed with our staff, but the patient did not display significant and continual signs of respiratory distress to necessitate this. While the patient was in the ICU, the result of the SARS-CoV-2 NAAT was positive for detection of the virus on 2 April 2020.

OUTCOME AND FOLLOW-UP

The patient remained in the ICU for 4 days and was subsequently downgraded to the general floor when it was felt that her respiratory status was improving, as she no longer required CPAP. On discharge on 8 April 2020, 10 days following admission, the patient endorsed that she had regained a majority of her sense of smell and that her sense of taste was greatly improved, although she did state foods did taste 'excessively salty' but no longer tasted metallic as noted before. She was not retested for SARS-CoV-2 prior to discharge but was advised to self-quarantine for 14 days on returning home. To limit exposure to the patient's primary care physician, the patient was instructed to call her physician as an outpatient to review her hospitalisation. She was instructed to return to the emergency room only if she experienced severe symptoms of respiratory distress or other alarming symptoms. A timeline detailing our patient's clinical course in relation to her gustatory and olfactory complaints is shown in figure 3.

DISCUSSION

SARS-CoV-2, a betacoronavirus, is an enveloped positive sense RNA virus⁷ that first arose in Wuhan, China, in December 2019. Officially declared a pandemic on 11 March by the WHO,⁸ COVID-19, caused by the novel coronavirus SARS-CoV-2, has affected over 2.4 million patients globally and resulted in over 169 000 deaths as of 20 April 2020.⁴

Throughout recent weeks, reports of anosmia as a symptom of COVID-19 have flooded the media. Otolaryngologists around the globe have reported a significant number of patients with COVID-19 presenting with olfactory dysfunction,⁹ but scientific data have proven that a significant association has been

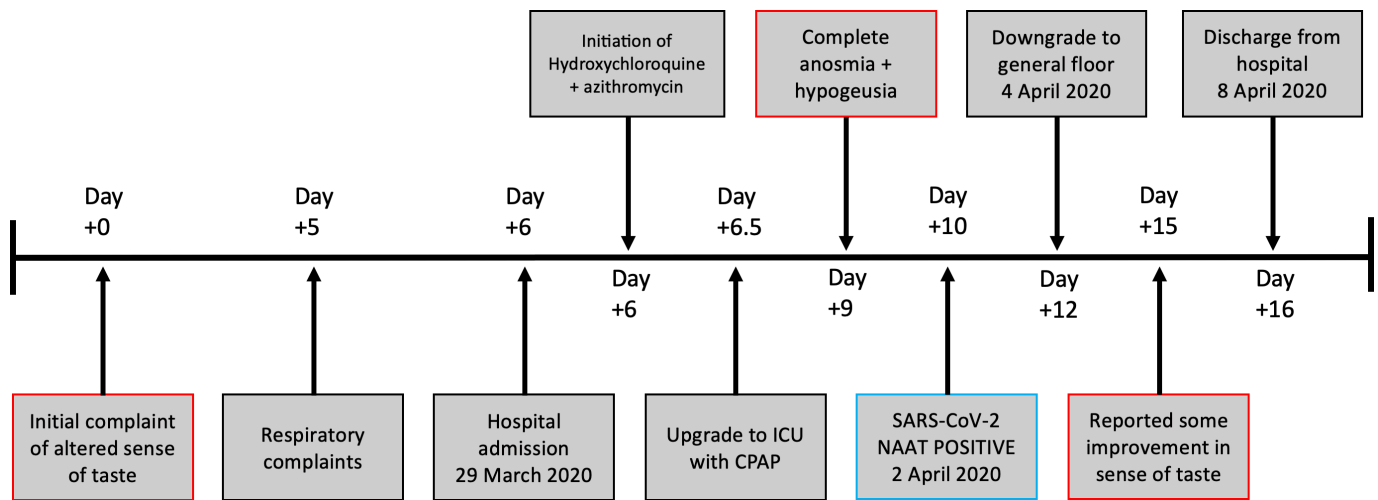


Figure 3 Timeline of our patient's clinical course with COVID-19. CPAP, continuous positive airway pressure; ICU, intensive care unit; NAAT, nucleic acid amplification test.

limited. A recent study in Italy using a patient questionnaire found that approximately one-third (20 of 59) of patients hospitalised with COVID-19 reported some degree of olfactory or gustatory dysfunction.¹⁰ Another recently accepted publication also involving olfactory and gustatory questionnaires was conducted at 12 European hospitals.¹¹ Among the 417 mild-to-moderate European patients with COVID-19 involved in the Lechien *et al* study, 85.6% and 88.0% reported olfactory and gustatory dysfunction, respectively. The majority (65.7%) of patients reported olfactory dysfunction occurring after the appearance of general ears, nose and throat symptoms; however, 11.8% of patients in this study reported olfactory dysfunction appearing before any other symptoms, suggesting anosmia may be important for early COVID-19 detection. They did not assess the prevalence of gustatory dysfunctions appearing as the first symptom, similar to how our patient presented. Additionally, olfactory dysfunction was not significantly associated with rhinorrhea or nasal obstruction,¹¹ hinting that the mechanism by which SARS-CoV-2 causes anosmia may be distinguishable from that of other common URI-causing viruses. However, Lechien *et al* did find significant associations between olfactory outcomes and several variables, including a significant association between fever and anosmia ($p=0.014$). Furthermore, women were proportionally more affected by hyposmia or anosmia compared with men ($p < 0.001$).¹¹ While more data are needed to determine if gender is a predisposing factor to the development of anosmia, the predilection for women in this study may be explained by sex dimorphisms in the olfactory bulb itself. A past study involving postmortem brains conducted in Brazil found that women have more neurons in the olfactory bulb.¹² The higher susceptibility of women to develop olfactory and subsequent gustatory dysfunction may also be related to sex differences in inflammatory cytokine production.¹³ Future studies exploring gender and additional demographic differences in patients with COVID-19 who experience anosmia are warranted.

The study of anosmia in COVID-19 has not been limited to Europe. Using a questionnaire sent out to over 10 000 residents in all provinces of Iran, a study that is now in preprint found that there is a significant correlation between anosmia and COVID-19 in the different provinces.¹⁴ However, reports of anosmia in Asia have not been robust. To our knowledge, Mao *et al*'s study, which details the neurological manifestations of 214 patients hospitalised with COVID-19 in Wuhan, China,

is one of the only studies that mention olfactory and gustatory dysfunction as symptoms associated with SARS-CoV-2.¹⁵ In contrast to the European studies, only 5.1% and 5.6% of patients in Mao *et al*'s study reported hyposmia and hypogeusia, respectively.¹⁵ Earlier studies originating from the virus' original epicentre of Wuhan have failed to mention effects on olfactory and gustatory sensation at all.^{16,17} This evokes many questions regarding the significance of anosmia and why it seems to be so prevalent in European populations yet hardly addressed in Asian papers. One explanation may be explained by variation in the SARS-CoV-2 genome. Analyses have revealed two major types of SARS-CoV-2, S and L, which are defined by their single-nucleotide polymorphisms.¹⁸ The L type was more prevalent in early stages of the outbreak in Wuhan, but its frequency has decreased.¹⁸ Emerging studies have also demonstrated continued evolution of SARS-CoV-2 in regard to its surface proteins, particularly the spike glycoprotein.^{19,20} This glycoprotein is necessary for binding cell receptors and thus determines host tropism,^{19,20} which may explain the potential clinical differences between patients of distinct demographic areas. Another possibility is that patients with COVID-19 in the Asian population in fact did have anosmia with associated hypogeusia and dysgeusia, yet these symptoms went un-noticed or under-reported. Unlike the loss of sight, which is readily apparent to others, anosmia can be particularly insidious and go unnoticed. As in the case of our patient, she did not realise she had anosmia until her perception of flavour and ability to enjoy foods were affected. For patients who eat primarily bland foods, such as white rice, which is a staple of the Chinese diet, anosmia and its subsequent impairment on retronasal olfaction may not be evident. The need for further scientific study involving validated smell tests to determine the significance is apparent. The implications of hyposmia and the overall use of olfactory performance measures to either support or diagnose the prognosis in COVID-19 go beyond the acute disease state itself. It is well known in the literature that individuals with persistent olfactory dysfunction are at particular risk for nutritional deficiencies, development of depression and other psychiatric disorders, and the inability to detect certain 'warning/danger' odours like natural gas, smoke, spoiled foods and other noxious gases.²¹ On 22 March 2020, a statement released from the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), 'Anosmia, hyposmia, and dysgeusia in the absence of other respiratory disease such as

Unusual association of diseases/symptoms

allergic rhinitis, acute rhinosinusitis, or chronic rhinosinusitis should alert physicians to the possibility of COVID-19 infection and warrant serious consideration for self-isolation and testing of these individuals'. On 26 March, the AAO-HNS released an anosmia reporting tool to assess for the significance of these symptoms in the diagnosis and progression of COVID-19.²² In a study analysing the first 237 of the tool's entries, Kaye *et al* found that anosmia was present in 73% of subjects prior to COVID-19 diagnosis and was the initial symptom in 26.6%. The most common symptoms to present before anosmia included cough (41%), malaise (39%), fever (38%) and headache (37%). Gastro-intestinal (GI) distress was the least likely symptom to present before anosmia, occurring in 10% of patients.²³ Similar to olfactory dysfunction, patients with COVID-19 presenting with GI symptoms have garnered particular media attention and have been subject to a recent study. In a study conducted among three hospitals in China, 18.6% of patients with COVID-19 presented with a GI-specific symptom, including diarrhoea, vomiting or abdominal pain. They also found that patients with COVID-19 may present with digestive symptoms, even in the absence of respiratory symptoms, although this occurred only in <1% of patients.²⁴ Similarly, in a study conducted in the USA involving 116 patients with confirmed SARS-CoV-2 infection, 31.9% of patients reported GI symptoms. This included loss of appetite (22.3%), nausea/vomiting (12.0%) and diarrhoea (12.0%) as the most common GI symptoms. None of the patients in this study developed isolated GI symptoms or GI symptoms as an initial manifestation of SARS-CoV-2 infection.²⁵ Although more data are needed, it seems that anosmia and hypogeusia may be more likely as initial symptoms in COVID-19.

Additional studies using objective olfactory and gustatory tests are necessary to establish the significance of anosmia and hypogeusia in patients with COVID-19. Nonetheless, preliminary research suggests that gustatory or olfactory complaints during a viral pandemic should not be ignored. In a study based in the USA using a survey sent out to both patients positive for COVID-19 and patients negative for COVID-19 with influenza-like symptoms, smell and taste loss were reported in 68% (40/59) and 71% (42/59) of subjects positive for COVID-19, respectively, compared with 16% (33/203) and 17% (35/203) of patients negative for COVID-19 ($p < 0.001$). Their results showed these chemosensory impairments were at least 10-fold more common in COVID-19-positive cases than COVID-19-negative cases, both presenting with similar influenza-like symptoms.²⁶ While the authors of this study did not reveal how many of these patients tested positive for influenza virus,²⁶ past studies have demonstrated that influenza is not significantly associated with change in smell.²⁷ Furthermore, postviral olfactory disorders due to other common viruses has an estimated prevalence of around 11%–40%,²⁸ which appears much less common than that seen with SARS-CoV-2 infection according to existing studies. Future research should also investigate the frequency of olfactory and gustatory dysfunctions in patients infected with influenza and other common viruses, in order to confirm the significance of its correlation with COVID-19.

Our unique patient case and the aforementioned literature highlight the importance of the physicians' ability to identify these subtle and sometimes unnoticed symptoms of this pandemic-creating virus. Peer-reviewed scientific literature is needed to further elucidate this early finding and to better understand the overall clinical course of SARS-CoV-2.

Contributors LEM contributed to project conception, writing/manuscript preparation: writing the majority of the initial draft as well as contributing to draft

Patient's perspective

This section highlights the patient's direct quotes regarding the initial presentation of her disease, the progression that led her to the ICU and her eventual improvement and discharge from the hospital.

- ▶ 'My husband was initially sick with what we thought was a cold. We were keeping up with the COVID-19 news and did not think that his symptoms could be it, because other than going to the grocery store, we had no direct contact with anyone. I then started to get really winded and began to cough. It was not until I spoke to the doctor at the hospital when I realized that my sense of taste and smell were off. Everything I was eating tasted off although they were recipes I made frequently. I did not know that my loss of smell was related to COVID'.
- ▶ 'When the doctors told me I may have COVID I was very nervous and feared for my life. Everything that I heard on the news made me even more concerned about this. I had also wondered if my husband did in fact have COVID in the first place but got over it'.
- ▶ 'I am thankful to have noticed early on to come to the hospital when I started having issues breathing as I believe my outcome would be a lot worse hadn't I called 911'.

Learning points

- ▶ Anosmia, dysgeusia and hypogeusia appear to be early presenting symptoms of COVID-19 in select patients that may occur prior to respiratory symptoms.
- ▶ While only recently added to the Centers for Disease Control and Prevention's list of symptoms and not yet considered stand-alone symptoms that warrant COVID-19 testing, new-onset anosmia, hypogeusia and/or dysgeusia (especially in the absence of nasal congestion) should prompt strict self-isolation to limit presumptive viral spread.
- ▶ For many, the experience of smell and its lack thereof can be particularly insidious and go relatively unnoticed without large disruption in day-to-day life.
- ▶ As clinicians, we need to be keen on these subtle and overlooked symptoms of COVID-19, especially when objective tests for anosmia are not readily available to most providers.
- ▶ Although purely anecdotal evidence for the relationship between COVID-19 infection and the symptoms of hyposmia and hypogeusia, these remain concerning symptoms and prompt further investigation.

revisions. In addition, she served as project administrator. She, along with all three coauthors, gave final approval of the version to be published. EB contributed to project conception and writing/manuscript preparation by writing portions of the initial draft (wrote most of the case presentation and patient perspective sections.) He also contributed to critical review, commentary and revisions. All direct patient contact, history-taking and patient quotes were obtained by EB. He, along with all three coauthors, gave final approval of the version to be published. EP contributed to the project by serving as project supervisor as the attending physician taking care of the patient. His roles also included writing/manuscript preparation, specifically critical review, commentary and revisions, and final approval of the version to be published.

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