Ear, Nose & Throat Journal
2020, Vol. 99(9) NP94–NP98

DOI: 10.1177/0145561320940119
journals.sagepub.com/home/ear
SAGE

Acute Olfactory Dysfunction—A Primary Presentation of COVID-19 Infection

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Abstract

COVID-19 is a zoonotic illness caused by a new strain of coronavirus and has recently been declared a pandemic by the World Health Organization, with an estimated fatality rate of 1% to 2%. Early identification and isolation of patients in the preliminary infective stage has been a mainstay of most governmental strategies in order to limit transmission. Four otherwise healthy patients presented to a specialist open access Ear, Nose & Throat Clinic in central London with acute total or subtotal loss of their sense of smell in a single one-week period, coinciding with rapid escalation of COVID-19 infection in the indigenous population. The diagnosis was confirmed by the validated University of Pennsylvania Smell Identification Test (UPSIT) in 3. Endoscopic examination and magnetic resonance imaging (2 cases) excluded a range of alternative potential pathological conditions. Covid-19 antibody testing carried out 6 to 8 weeks after the onset of nasal symptoms showed positive immunoglobulin G antibodies in 3 of the 4 patients. Acute severe anosmia is therefore almost certainly an unusual presenting local nasal feature of a COVID-19 viral infection. All 4 patients achieved significant partial olfactory recovery by one week after treatment with subjective ratings of 40% to 85% of normal (mean 60%) and complete olfaction recovery after 2 to 3 weeks in all 4 patients. The significance, possible pathogenesis, and public health implications are highlighted and discussed.

Keywords

anosmia, olfactory neuritis, olfactory dysfunction, COVID-19, SARS-CoV-2, anosmia treatment, University of Pennsylvania Smell Identification Test (UPSIT)

Introduction

In 10 weeks, a global health and economic crisis unprecedented in modern times has been precipitated by a new strain of severe acute respiratory syndrome coronavirus (SARS-CoV-2), causing a human illness named COVID-19 (coronavirus disease 2019). By mid-March 2020, there had been over 180 000 confirmed cases and 7000 deaths (fatality rate 1%-2%) in over 50 countries.[1] The subsequent exponential explosion of infected cases prompted the World Health Organization to declare the illness a pandemic. Early identification and isolation of patients in the infective stage has been an important strategy to reduce transmission. However, the effectiveness of this approach may have been limited by patients with asymptomatic, atypical, or very mild disease who evade detection by conventional screening protocols.

Acute olfactory neuritis is an uncommon cause of sudden severe or total loss of the sense of smell. Four otherwise healthy patients, aged 28 to 37 years old, presented to a specialist open access Ear, Nose & Throat Clinic in central London with acute loss of their sense of smell and taste disturbance in a single one week period. Two cases were completely asymptomatic otherwise, while 2 patients reported mild nasal congestion for a few days before the onset of anosmia. None had suffered a pyrexia, cough, or other respiratory symptoms consistent with current UK Department of Health guidelines for self-solation. Specific Covid-19 antibody tests[2] carried out 6 to 8 weeks after the onset of olfactory symptoms showed immunoglobulin G (IgG) positive antibodies in 3 of the patients, confirming a previous Covid-19 infection. The Biozek antibody test has a 98% specificity for IgG antibodies and no known false positives. During the current pandemic and in the absence of alternative

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Received: March 27, 2020; revised: June 11, 2020; accepted: June 12, 2020

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pathology, by far the most plausible etiology for this large cluster of cases is therefore an acute COVID-19 viral infection.

Case Reports

Case 1

A 37-year-old Italian man presented with severe loss of his sense of smell 6 days before, with associated slight nasal congestion. There was no complaint of a pyrexia, cough, or other chest symptoms. Nasendoscopy showed good access to the right olfactory niche. There was no sign of local congestion, infection, polyps, or other pathology. A University of Pennsylvania Smell Identification Test (UPSIT)[3], which is a validated olfactory assessment, gave a score of 27/40, suggesting a moderate degree of microsmia or subtotal anosmia. A magnetic resonance imaging (MRI) scan showed normal olfactory bulbs and cribriform plates with minimal mucosal thickening in the ethmoid sinuses.

A diagnosis of an acute viral olfactory neuritis was made, most likely due to the COVID-19 pandemic. Treatment with oral steroids and topical steroid inflammatory drops was commenced. At follow-up one week later, the patient reported a subjective 50% recovery of his sense of smell, without new symptoms of pyrexia, cough, or breathing difficulties. Covid-19 antibody testing 8 weeks later showed positive IgG antibodies. He reported that his sense of smell had subjectively recovered completely by about 2 to 3 weeks after presentation.

Case 2

A 33-year-old fashion designer presented in a distressed state, with a 7-day history of acute total loss of her sense of smell. There was no complaint of rhinorrhea, nasal congestion, or other features of a recent URTI. She was otherwise well without a pyrexia, cough, or chest symptoms. A self-administered test of olfaction with Clive Christian X for men, an extremely strong pungent perfume, indicated subjective total anosmia. Nasendoscopy showed good access to the olfactory niche, with no evidence of infection, nasal polyposis, or any other pathology. An MRI scan showed normal olfactory bulbs and cribriform plates with minor mucosal thickening of the ethmoid air cells.

A diagnosis of acute olfactory neuritis, almost certainly due to the pandemic COVID-19 virus, was made and treatment commenced with high-dose oral steroids and topical steroid nasal drops. Two days after commencing treatment, she noted a definite improvement in her sense of smell, with further subjective recovery to 40% of normal after one week and complete recovery by 2 weeks. In addition, there were no new symptoms of a pyrexia, cough, or respiratory compromise. Covid-19 antibody testing was carried out 6 weeks after the onset of nasal symptoms, which was negative for IgG and immunoglobulin M antibodies.

Case 3

A 28-year-old marketing manager presented with complete loss of smell and taste 5 days before. Three days before the onset of anosmia, she had experienced mild URTI symptoms of nasal congestion, clear rhinorrhea, sporadic sneezing without an associated cough, or pyrexia. By day 3, her mild URTI symptoms had completely resolved, but a precipitous reduction in her sense of smell and taste occurred overnight. On examination, she was apyrexial. Rigid nasoendoscopy showed rhinitis with clear mucus in the nasal cavity without signs of active infection. There were no visible suspicious lesions and the olfactory niches were normal. Her UPSIT olfactory score was 19/40, indicating severe microsmia.

A diagnosis of highly likely Covid-19 viral infection causing olfactory neuritis was made. She had previously used a nasal decongestant and neti pot nasal irrigation for 2 days without benefit. Betnesol and ephedrine nasal drops were prescribed and a computed tomography (CT) scan recommended if symptoms persisted. At follow-up, 3 days after commencing treatment, she reported a 30% subjective improvement in olfactory function, which had improved to 85% by day 7, with complete recovery by 2 weeks. Computed tomography imaging was therefore not undertaken. Covid-19 antibody testing carried out 6 weeks after the onset of nasal symptoms showed positive IgG antibodies, confirming a previous Covid-19 viral infection.

Case 4

A 31-year-old male teacher presented with a 5-day history of the sudden onset of complete loss of his sense of smell and taste. He had no previous symptoms of an upper respiratory tract infection. He did not report a pyrexia, cough, or other associated respiratory symptoms. On examination, he was apyrexial. Rigid nasendoscopy showed a minor degree of nasal congestion, but no pus or polyps. The olfactory recesses were clear with no sign of any mucosal swelling. He was seen the day after commencing treatment, when his UPSIT score was 21/40, indicating severe microsmia.

A diagnosis of acute viral olfactory neuritis was made, very probably due to the pandemic COVID-19 virus. The patient was advised to self-isolate. Anti-inflammatory treatment with oral prednisolone for 3 days followed by topical intranasal steroid drops was commenced and CT/MRI imaging recommended in the absence of recovery. No further symptoms of pyrexia, cough, or shortness of breath developed, and he continued to work from home teaching by virtual technology. By the sixth day of treatment, the sense of smell had subjectively improved to 60% of normal with complete recovery reported by 2 weeks after the onset of nasal symptoms. Imaging was therefore not undertaken. Covid-19 antibody testing carried out 6 weeks after the onset of nasal symptoms showed positive IgG antibodies, confirming a previous Covid-19 viral infection.

Discussion

Severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus (MERS-CoV) caused previous coronavirus epidemics, with both nasal and pulmonary symptoms. COVID-19 has also proved to be a highly infectious virus, assisted by the relative paucity of early clinical

symptoms. Some people infected with the coronavirus have no clinical symptoms at all, as in 2 of our case series, but may still be highly infectious. More commonly, patients report a low-grade fever, body aches, cough, nasal congestion, runny nose, and sore throat, symptoms which closely parallel more conventional viral URTIs and also previous SARS and MERS infections. Occasionally, COVID-19 causes more severe symptoms such as a very high temperature, severe cough, shortness of breath, and pneumonia resulting in an acute respiratory distress syndrome.

Because of the paucity of early symptoms, the incubation period of COVID-19 infection is unknown. Symptoms are considered to appear between 3 and 14 days after exposure, averaging 5 days. Likewise, the duration of infectivity is uncertain, with commonly reported ranges between 7 and 14 days. Infectivity is thought to peak as symptoms start. The COVID-19 virus is detectable outside the body for up to 3 hours in aerosols, 24 hours on cardboard and up to 2 to 3 days on plastic and stainless steel,[4] features which also facilitate widespread and rapid transmission.

Post-viral olfactory dysfunction is caused by inflammation with/without edema of the olfactory receptors and adjacent mucosa and/or neurodegeneration of olfactory neural system. Influenza viruses, parainfluenza viruses, rhinoviruses, and respiratory syncytial viruses have long been associated with human URTIs and olfactory disturbance, but few cases cause persistent severe or total olfactory neurodysfunction. Although post-viral acute olfactory neuritis is a well-recognized cause of anosmia, it is relatively uncommon in Ear, Nose & Throat practice, especially when one considers the extremely high frequency of upper respiratory tract infections in human populations, which has been estimated at 3 per annum in adults.[5,6] A recent comprehensive review of viral URTI's fails to mention olfactory neuritis as a possible sequelae at all.[7] Universal early nasal symptoms are congestion and mucoid rhinorrhea, both of which result in an impaired sense of smell due to obstruction,[8] because the inflammatory mucosal edema prevents the physical access of stimulatory molecules to the olfactory niche. It is only when this early congestion is clearing after 7 to 10 days that severe olfactory issues may become apparent. These patients do not usually, therefore, present in the acute phase.

The first identification of coronavirus in the nasal secretions of a patient with olfactory impairment was published by Suzuki et al in 2007.[9] However, acute loss of smell is not mentioned as a feature in any previous medical reviews of SARS and MERS case.[10,11] In fact, an extensive literature search only reveals one reported case of olfactory neuropathy with SARS,[12] discussed below. Eliezer et al[13] very recently reported a single case of complete anosmia, assessed by subjective clinical olfactory testing, associated with COVID-19. Last month, a non-peer-reviewed report in Italy describes 6 patients with sudden hyposmia, documented by "le nez du vin" subjective clinical assessment, as the only or main manifestation during the recent COVID-19 outbreak.[14] A recent statement by ENT UK lists anecdotal reports of hyposmia in South Korea in about 30% of COVID-19 positive cases, where testing has been more widespread, and significant numbers of similar cases in China, Germany, and France.[15] However, anosmia/severe hyposmia invariably occurs as part of a constellation of Covid-19 symptoms in these patients rather than as an isolated presenting feature as in our present case series.

COVID-19 virus appears to share similar features with the SARS and MERS coronaviruses in respect of disease incubation and duration times, and the potential for severe pneumonitis and respiratory distress. However, our and other reported cases suggest that COVID-19 virus displays a significantly higher propensity for causing inflammatory damage to the nasal olfactory receptors and adjacent mucosa resulting in severe hyposmia/anosmia. In the case reported by Eliezer et al,[13] a CT scan showed bilateral inflammatory obstruction of the olfactory clefts, a feature which was not present on MRI skull base imaging in the 2 cases undergoing imaging in the present series. Moreover, endoscopic examination in all of our cases confirmed an exposed and open olfactory niche. These features are consistent with either an olfactory neuritis etiology or a very localized inflammatory response of the olfactory niche/cribriform plate region. Inflammatory edema of the nerve sheath could potentially result in neural dysfunction from local compression as the fibers pass through the cribriform plate, analogous to facial nerve dysfunction developing from inflammatory compression, and Wallerian degeneration of nerve fibers in the fallopian canal during a Bell's palsy.

The COVID-19 virus displays particularly aggressive activity in the lower respiratory tract, which results in characteristic CT scan features.[16] Angiotensin-converting enzyme 2 (ACE2) is the main human receptor for the SARS S glycoprotein. Although ACE2 protein is present in vascular endothelial and smooth muscle cells in all organs, studies show particularly high concentrations in lung alveolar epithelial cells and enterocytes of the small intestine.[17] Furthermore, ACE2 expression has been identified in the basal layer of the nasal mucosa and nasopharynx, though in lower concentrations. This ACE2 tissue disparity probably explains the more significant adverse effects on lung rather than nasal tissues.

COVID-19 shows exceptionally high levels of pro-inflammatory cytokines in the serum of patients hospitalized with respiratory compromise. Cytokine storm, the massive overproduction of immune cells in response to infection, appears to be associated with the severity of COVID-19.[18] A comparable hyper-inflammatory local tissue response, driven by virus-ACE2 interaction, involving the local blood vessels, mucosa, and sensory receptors of the olfactory niche in the superior nasal cavity could explain the development of acute and severe hyposmia/anosmia reflected in our series. The early rapid improvement of olfactory function in all our 4 patients after topical anti-inflammatory and decongestant treatment is more consistent with an acute local inflammatory pathogenesis in the superior nasal cavity, rather than significant neurodegeneration.

Hwang reported the only previous case of olfactory dysfunction with a coronavirus severe SARS.[12] A 27-year-old female, who had largely recovered otherwise, noted the acute onset of complete anosmia 3 weeks after disease onset. Her MRI brain scan did not show any nasal or anterior cranial/skull base pathology. The anosmia persisted for more than 2 years during follow-up, though no active treatment was given.

Several studies report significant spontaneous improvement in non-COVID-19 post-viral olfactory dysfunction of 32% to 35% over periods of 4 to 14 months.[19-24] Systemic and topical steroids,[22,23] vitamin B supplementation,[21] and intranasal insulin[23] have all been used to treat non-COVID-19 post-viral olfactory dysfunction with some degree of success. Our preliminary early treatment results in COVID-19 cases showed significant improvement in olfactory function in all 4 cases, usually commencing within 48 hours with subsequent complete recovery by 2 to 3 weeks. This rapid recovery is consistent with a local severe inflammatory response of the local nasal mucosa and/or a reversible olfactory neuritis rather than an underlying neuropathy as in the previously reported SARS patient.[11] Treatment outcomes are not provided in any of the recent subjective and anecdotal COVID-19 hyposmia reports.[13-15]

The absence of associated respiratory symptoms and clinical pulmonary disease reflects the relatively benign nature of putative solitary COVID-19-related olfactory dysfunction. It seems likely that there is a broad spectrum of COVID-19-related symptoms, probably more so than previously seen in SARS/MERS epidemics. Our small series corroborates very recent reports suggesting olfactory dysfunction as a sole presenting symptom. Although these patients present with a mild form of COVID-19 disease, there is no reason to suspect that they are not as infectious as those with more widely recognized symptomatology, such as fever and/or cough. The recognition, identification, and isolation of these patients, who may be more prevalent in the general population than previously suspected, would therefore be critical as a public health measure to prevent further spread of this potentially lethal disease.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

1. World Health Organization. 2020. www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Inzek International Trading. 2020. http://biozek.com/coronavirus-covid-rapid-test/
3. Doty RL, Shaman P, Dann ML. Development of the University of Pennsylvania Smell Identification Test: a standardised microencapsulated test of olfactory function. *Physiol Behav*. 1984;32(3):489-502.
4. Van Doremalen N, Morris DH, Holbrook MG, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. 2020;382(16):1564-1567.
5. Arroll B. Common cold. *BMJ Clin Evid*. 2008;2008:1510. [PMC free article: PMC2907967] [PubMed: 12588210].
6. Winther B, Gwaltney JM, Mygind N, Hendley JO. Viral-induced rhinitis. *Am J Rhinol*. 1998;12(1):17-20.
7. Thomas M, Bomar PA. Upper respiratory tract infection. *StatPearls*. StatPearls Publishing; 2020.
8. Akerlund A, Bende C, Murphy C. Olfactory threshold and nasal mucosal changes in experimentally induced common cold. *Acta Otolaryngol*. 1995;115(1):88-92.
9. Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with post-viral olfactory dysfunction. *Laryngoscope*. 2007:117(2):272-277.
10. De W, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. 2016;14(8):523-534.
11. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
12. Hwang CS. Olfactory neuropathy in severe acute respiratory syndrome: report of a case. *Acta Neurol Taiwan*. 2006;15(1):26-28.
13. Eliezer M, Hautefort C, Hamel AL, et al. Sudden and complete olfactory loss function as a possible symptom of COVID-19 [published online ahead of print April 8, 2020]. *JAMA Otolaryngol Head Neck Surg*. 2020. doi:10.1001/jamaoto.2020.0832
14. Marchese-Ragona R, Ottaviano G, Nicolai P, Vianello A, Carecchio M. Sudden hyposmia as a prevalent symptom of COVID-19 infection. *MedRxiv*. 2020. doi:10.1101/2020.04.06.20045393
15. Hopkins C, Kumar N. Loss of sense of smell as a marker of COVID-19 infection. *Br Rhinol Soc*. 2020. www.entuk.org/COVID-19
16. Zu ZY, Jiang MD, Xu PP, et al. Coronavirus disease 2019 (COVID-19): a perspective from China [published online ahead of print February 21, 2020]. *Radiology*. 2020.
17. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GV, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. a first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(3):631-637.
18. Heilmann S, Just T, Goktas O, Hauswald B, Hüttenbrink KB, Hummel T. Effects of systemic or topical administration of corticosteroids and vitamin B in patients with olfactory loss [in German]. *Laryngorhinootologie*. 2004;83(11):729-734.
19. Hendriks APJ. Olfactory dysfunction. *Rhinology*. 1988;26(4):229-251.

20. Reden J, Mueller A, Mueller C, et al. Recovery of olfactory function following closed injury or infections of the upper respiratory tract. *Arch Otolaryngol Head Neck Surg*. 2006;132(3):265-269.
21. Dai Q, Pang Z. Recovery of olfactory function in postviral olfactory dysfunction patients after acupuncture treatment. www.hindawi.com/journals/ecam/2016/4986034/
22. Seo BS, Lee HJ, Mo JH, Lee CH, Rhee CS, Kim JW. Treatment of postviral olfactory loss with glucocorticoids, ginkgo biloba and mometasone nasal spray. *Arch Otolaryngol Head Neck Surg*. 2009;135(10):1000-1004.
23. Stenner M, Vent J, Hüttenbrink KB, Hummel T, Damm M. Topical therapy in anosmia; relevance of steroid-responsiveness. *Laryngoscope*. 2008;118(9):1681-1686.
24. Rezaeian A. Effect of intranasal insulin on olfactory recovery in patients with hyposmia: a randomised clinical trial. *Otolaryngol Head Neck Surg*. 2018;158(6):1134-1139.