World Journal of Otorhinolaryngology-Head and Neck Surgery (2020) 6, S26—S32

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Review Article

Is SARS-CoV-2 (COVID-19) postviral olfactory dysfunction (PVOD) different from other PVOD?

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Received 28 April 2020; received in revised form 7 May 2020; accepted 8 May 2020
Available online 19 May 2020

KEYWORDS
Olfaction;
Olfactory disorders;
UPSIT;
SARS-CoV-2 (COVID-19);
Postviral olfactory dysfunction

Abstract *Background:* The SARS-CoV-2 virus continues to spread rapidly across the globe afflicting many with Coronavirus Disease 2019 (COVID-19). As the infection rates rise, a growing number of SARS-CoV-2 positive individuals have been reported to complain of olfactory disturbances at an alarming rate. Postviral olfactory dysfunction (PVOD) is a well-known phenomenon that may explain the olfactory dysfunction reported by SARS-CoV-2 infected individuals.
Methods: A scoping literature review was performed to identify studies that investigated the mechanisms of postviral olfactory dysfunction. Studies demonstrating pathophysiological, histological, immunochemical, and epidemiological outcomes of PVOD were included.
Results: Fourteen studies were included in addition to one international news article. Three studies reported destruction of the olfactory epithelium following intranasal inoculation of various viral strains in mice. Three studies isolated pathogenic, anosmia inciting viruses (Parainfluenza virus, Human Coronavirus, Rhinovirus) through nucleic acid amplification. Eleven studies demonstrated female predilection in patients with PVOD and COVID-19 associated olfactory dysfunction, of which the majority were over 50 years old.
Conclusions: PVOD and COVID-19 associated olfactory dysfunction demonstrates considerable similarities in epidemiological trends and disease sequela of other viruses to suggest identical

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.wjorl.2020.05.004

pathophysiological mechanisms. Further studies such as intranasal inoculation and histological biopsies are needed to support our hypothesis.

Introduction

The rapidly spreading SARS-CoV-2 virus continues to devastate the globe since its emergence in late 2019 and continues to afflict many with the deadly coronavirus disease 19 (COVID-19).[1] It behaves similarly to previous discovered known coronaviruses strains (SARS-CoV and MERS), viruses known to cause severe respiratory disease. However, the virus has also demonstrated a more indolent process, such as a short course of an upper respiratory infection (URI) in those that do not have multiple comorbidities.[1,2] Smell disturbance is common following a viral URI and as more is discovered about SARS-CoV-2, olfactory disturbances are becoming more apparent in this population, often in otherwise asymptomatic patients.[3] Anosmia, hyposmia, and dysgeusia in SARS-CoV-2 positive patients has been rapidly gaining attention throughout the medical sphere as another potential screening symptom. Multiple otolaryngologic associations have reported that rates of olfactory and gustatory dysfunction have been increasing at alarming rates too fast to be considered normal, especially in the setting of the current pandemic.[3,4]

Postviral olfactory dysfunction (PVOD) is one of the most common causes of olfactory dysfunction. Olfactory dysfunction typically results from head trauma, conductive (airway obstruction) disorders, or olfactory sensor neural disruptions.[5–8] The underlying pathophysiology of PVOD is poorly understood, however. A delay in seeking care, difficulty in isolating causative viruses, and the absence of standardized methods available to diagnose PVOD may all contribute to the challenging etiology.[9]

The current understanding and sequence of olfactory dysfunction following a viral URI begins as nasal mucosal inflammation, disrupting natural airway conduction within the nasal cavity, and inhibiting the delivery of odorants to the olfactory epithelium. The persistence of olfactory dysfunction following recovery from the URI is likely explained by direct damage to the olfactory epithelium and olfactory bulb by the virus itself.[5,6,10]

We review the existing literature on PVOD and compare it with the rapidly growing evidence of COVID-19 related olfactory dysfunction. Our purpose is to provide evidence that may suggest that SARS-CoV-2 infection is a likely cause of the increased rates of reported anosmia, hyposmia, and dysgeusia in SARS-CoV-2 positive patients.

Methods

A scoping literature review was performed starting on March 27, 2020. Articles reporting on viral olfactory dysfunction were collected by reviewing publications listed in the PubMed database. A search strategy was employed with the following search strings: "virus" OR "viral" OR "infectious" AND "postviral olfactory dysfunction" OR "viral anosmia" OR "viral hyposmia". We reviewed articles regarding viral-associated anosmia, the histological changes observed in humans and animals with PVOD, and PVOD related epidemiological studies. Reference lists of all obtained articles were examined for additional studies meeting inclusion criteria. In attempts to search for COVID-19 associated anosmia articles, the following search strategy in the PubMed database was employed with the following search strings: "SARS-CoV-2" or "2019-nCov" or "Coronavirus" or "COVID-19" and "Anosmia" or "hyposmia" or "loss of smell" or "smell". Given the recent appreciation of COVID-associated OD and expectation of limited peer reviewed publications, we also conducted a search through the gray literature in Medrvix, an archive for pre-print, non-peer reviewed manuscripts relating to the medical, clinical, and related health sciences. We also reviewed shared manuscripts listed on the American Academy of Otolaryngology- Head and Neck Surgery website. Three articles relating to COVID-19 associated olfactory dysfunction were obtained.

Results

The initial literature review with the first set of search strings yielded 81 abstracts. A review of potential abstracts identified 35 articles that described postviral olfactory dysfunction. Of these articles, 10 were unable to be translated into English and 14 did not have enough extractable data. The remaining 11 articles were included in the final review. The secondary literature review with the second set of search strings yielded 0 abstracts. Review through the gray literature yielded 3 articles that described COVID-19 associated olfactory dysfunction. One international news article was included that described COVID-19 epidemiological data. Given the expected heterogeneity in outcome metrics, no meta-analysis or statistical tests were performed.

Animal models

In animal models investigating PVOD, multiple authors demonstrate similar histological findings in olfactory epithelium and bulb following intranasal inoculation with different viral strains in mice.[11–13] Following intranasal inoculation with Sendai virus 52, a mouse counterpart to human parainfluenza virus, immunofluorescence revealed sparse apoptosis and decreased proliferation of the olfactory epithelium. Inoculated mice exhibited anosmia

behavior changes with failed buried food test challenges, where the degree of olfaction loss is quantified by failure or prolonged duration of the mice to find buried food pellets compared to control mice.[11] In the study done by Mori et al,[12] mice were inoculated with Influenza A R404BP strains. Histologically, the authors identified apoptosis of the olfactory neurons within the olfactory epithelium. In another study, histological changes were varied between the olfactory epithelium and the olfactory bulb in response to intranasal inoculation with Mouse Hepatitis Virus, a mouse counterpart to Human Coronavirus in the study done by Schwob et al. Minimal destruction was observed in olfactory epithelium in acute infection in contrast to significant degenerative spongiosis seen in the olfactory bulb (Table 1).[13]

Human models

Similar histological findings were observed in human olfactory epithelium following a viral illness in the studies done by Jafek et al, Yamagishi et al, Douek et al, and Moran et al. Though the causative virus was not identified in these studies, all subjects exhibited fairly identical histological patterns such as disorganization, scarring, and atrophy of the olfactory epithelium with respiratory tissue metaplasia. Marked reduction of olfactory epithelial density and receptors were also noted. The authors observed that hyposmic subjects had a lesser extent of olfactory epithelial destruction compared to anosmic subjects.[14–17]

Anosmia associated viral strains

Few authors have performed studies identifying the viral strains responsible for anosmia. Following intranasal inoculation with human coronavirus (229E), previously healthy adult subjects demonstrated atypical upper respiratory virus sequela of nasal obstruction and rhinorrhea, in addition to varying degrees of olfactory dysfunction ranging from mild dysosmiato complete anosmia as measured by butanol threshold tests.[10] Sugiura et al[18] deduced that the likely viral strain responsible for most PVOD was Parainfluenza virus. They compared epidemiologic incidence rates of PVOD with the incidence rates of various anosmia-associated viruses. They found that the incidence rates of PVOD and parainfluenza virus were nearly identical. Increased antibody titers to Parainfluenza virus were also obtained in affected individuals, further supporting their observations. Suzuki et al. Wang et al and Landis et al isolated various viral strains in patients that presented with acute PVOD. With a combination of reverse transcriptase polymerase chain reaction (RT-PCR) and PCR performed on specimens obtained from nasal discharge, turbinate epithelium, or cerebrospinal fluid, multiple viral strains were identified including but not limited to Human Coronavirus, Rhinovirus, and Parainfluenza virus (Table 2).[19–21] Potter et al[22] analyzed the seasonal variation of PVOD in 587 patients in both influenza and non-influenza cohorts. They found that non-influenza related PVOD had the highest prevalence between March through June.

Epidemiologic observations

In epidemiological studies of PVOD, the majority of which were in Asian countries, considerable common alities exist within those afflicted. Although PVOD may occur at any age, it seems more prevalent in those that are over 50, with a predilection toward women. 77.5% of patients diagnosed with PVOD were women (Table 3). The authors describe that the duration of olfactory dysfunction or rate persistence is unpredictable and does not appear to have any association with age, race, or gender.[7,18,20,23,24]

COVID-19 associated olfactory dysfunction

Given the relatively new appreciation of COVID-19 associated olfactory dysfunction, there have not been any animal or human studies using this strain to induce anosmia. Epidemiological surveys conducted in Daegu City, South Korea report 15% of SARS-CoV-2 positive individuals have new onset olfactory or gustatory abnormalities, of which 61.3% were between the ages of 20 and 40.[25] In a retrospective case series by Mao et al[26] neurological manifestations in SARS-CoV-2 positive patients were investigated. Their study reports that 5.1% and 5.6% experienced hyposmia and hypogeusia, respectively; which were among the most prevalent peripheral nervous system impairments. 58% were over the age of 50 and 59.3% were female within their entire cohort. Conducted within 4 weeks after the country declared COVID-19 pandemic status, an epidemiological survey in Iran suggests 76% of COVID-19 infected patients experienced olfactory dysfunction following a flu-like illness, of which 71% were women.[4] This sudden surge in olfactory dysfunction coincided with the country's rapid increase inSARS-CoV-2 positive cases. The average age of those surveyed was 32.5 years old. In a large European multi-center epidemiological study by Lechien et al[3] they found that 85.6% of laboratory confirmed SARS-CoV-2 patients complained of new onset olfactory dysfunction; 88% complained of gustatory dysfunction. Among those studied, females were disproportionately affected at 63% (Table 4).

Table 1 Histological and immunofluorescent changes following intranasal inoculation of various viral strains in mice.

Authors	Animal	Inciting Virus	Human Virus Counterpart	Histology/Immunofluorescence
Tian[11]	Mouse	Sendai Virus 52	Parainfluenza	Apoptosis and decreased proliferation of olfactory epithelium
Mori[12]	Mouse	Influenza A R404BP	Influenza A	Apoptosis of olfactory neurons
Schwob[13]	Mouse	Mouse Hepatitis Virus	Human Coronavirus	Scant turnover of olfactory epithelium, spongiosis of olfactory bulb

Table 2 Pathogenic viruses identified in patients with PVOD utilizing various isolating techniques.

Authors	Inciting or Pathogenic Virus	Viral Isolation Method
Åkerlund[10]	Human Coronavirus 229E	Intranasal inoculation with HCV 229E
Sugiura[18]	Parainfluenza virus[a]	Combination of Epidemiologic data, identification of viral traits, viral antibody titers
Suzuki[19]	Rhinovirus, Coronavirus 229E, Parainfluenza virus[a]	PCR, RT-PCR of nasal discharge
Wang[20]	Parainfluenza virus	RT-PCR of turbinate epithelium
Landis[21]	Herpes Simplex Virus Type 1	PCR of CSF

PVOD: postviral olfactory dysfunction.
[a] Additional viral strains identified including: Picornavirus and Ebstein-barr virus.

In this study, 73% report resolution of olfactory function within 8 days, however 63% of patients report persistent olfactory loss after resolution of their URI. It appears that the onset of olfactory dysfunction was nonspecific, such that it appeared before, during, or after URI symptoms.[3] A cohort study by Moein et al[27] quantified the presence of olfactory dysfunction using the University of Pennsylvania Smell Identification Test (UPSIT) in 60 COVID patients and corresponding age-matched controls. 98% of COVID patients had some degree of olfactory dysfunction with statistically significant decreased UPSIT scores compared to their controls (Table 4).

Discussion

Viral similarities in disease sequela

SARS-CoV-2 shares similarities to other PVOD causing viruses. Influenza virus, rhinovirus, human coronavirus, parainfluenza virus, and metapneumovirus among others have the capability of causing pneumonia and severe respiratory symptoms in susceptible populations but more frequently, these viruses mainly causes mild URI. Sporadically, these viruses cause olfactory dysfunction.[18–20,28,29] Similarly, SARS-CoV-2 is seen to demonstrate a similar range of disease severity; from otherwise benign anosmia to severe pneumonia and acute respiratory distress syndrome.[1,2]

Epidemiological similarities

Epidemiologic studies have demonstrated certain similarities between PVOD groups. Reviewing the literature, PVOD tends to affect women more when compared to men, more so as women approach older age. Certain presumptions have been made regarding these findings, such that estrogen may play a protective role in olfaction. Deems et al identified that the majority of women with PVOD in their study were postmenopausal, supporting estrogen's protective role in olfaction. In another study, when postmenopausal estrogen therapy was accounted for in women diagnosed with PVOD, the women taking estrogen had

Table 3 Epidemiological data of PVOD cases from various countries.

Authors	Country	n (Total PVOD cases)	Mean Age (years)	Gender Predilection (%)
Mori[23]	Japan	190	55	Female (87.4)
Liu[7]	China	143	47	Female (70.6)
Sugiura[18]	Japan	266	50–60[a]	Female (86)
Wang[20]	South Korea	25	51	Female (80)
Deems[24]	United States of America	192	55	Female (63.5)
Totals	—	816	—	77.5%

POVD: Postviral olfactory dysfunction.
[a] Predominant age range diagnosed with PVOD.

Table 4 Epidemiological data of COVID-19 associated olfactory dysfunction from various countries.

Authors or Sources	Country	N (total COVID cases)	Age Distribution [years, (%)]	Gender Predilection (%)	Olfactory Dysfunction (%)
JoongAng[25]	South Korea	3191	20–40 (61.3)	n.m.	15.3
Mao[26]	China	214	>50 (58)	Female (59.3)	5.1
Bagher[4]	Iran	10 069	32.5*	Female (71)	76
Lechien[3]	Belgium, France, Italy, Spain	417	36.9*	Female (63)	85.6
Moein	Iran	60	46.55*	Male (66)	98
Totals	—	13 951	—	56.8	56

n.m.: not mentioned; *mean age.

better olfactory detection than those who were not taking estrogen. Furthermore, it was observed that women had better olfaction performance status compared to men.[18] From preliminary data presented, SARS-CoV-2 infection demonstrates considerable epidemiological similarities, especially the considerable evidence of women being disproportionately affected. As already mentioned, this finding may be in part from the protective effect of estrogen, possibly in its role in reducing inflammation.[3] One observable difference is that COVID related olfactory dysfunction seems to predominantly affect the younger population. Selection bias may be a possible explanation for the older age observed by Mao et al[2] granted their cohort consisted of acutely ill, hospitalized patients. Considering that COVID-19 disproportionately causes more severe symptoms in the elderly that may require hospitalization, the presence of olfactory dysfunction in younger and non-hospitalized patients may not be fully represented. Persistence and recovery rates were only measured in one study (Leichen et al), therefore only limited comparisons can be made. Although duration and recovery rates of COVID related olfactory dysfunction have been measured, prognostic factors remain inconclusive unless additional long-term follow-up studies are conducted. The pathophysiology for PVOD is definitionally separate from olfactory dysfunction caused by allergic rhinitis and rhinosinusitis. Several patients with COVID related olfactory dysfunction were reported to have rhinitis, rhinosinusitis, or previous sinus surgery comorbidities — potentially confounding the incidence of viral induced olfactory dysfunction, considering previous PVOD studies intentionally excluded patients with conductive olfactory dysfunction. However, the presence of conductive olfactory dysfunction does not exclude a superimposed PVOD. Peak PVOD in non-influenza viruses coincides with the prevalence of COVID on the east coast of the United States. Thus, the increase in PVOD may be difficult to attribute solely to COVID when many viruses cause PVOD during this time period.

Histological changes reflect severity of olfactory disturbance

In the aforementioned animal studies, similar histological findings in the olfactory parenchyma is observed, irrespective of the viral strains chosen for intranasal inoculation. The animal models also demonstrate similar changes in anosmia related behavior, such that mice were incapable of detecting buried food compared to control mice following infection.[11] Almost identical histological changes in post viral human olfactory epithelium strengthens the hypothesis that nearly all viral strains associated with anosmia cause direct olfactory epithelial damage. The varying severities of olfaction dysfunction (hyposmia or anosmia) is proposed to reflect the degree of epithelial destruction, viral load, and viral serotype.[10,15,19,30] Certainly, a reduction in olfactory receptors within the olfactory epithelium would decrease odor binding capability. Furthermore, if extensive destruction occurs at the level of the olfactory bulb, a lack of signal transduction may contribute to the severity of olfactory dysfunction as well.[13] These findings may be an indicator to the varying degrees of olfactory dysfunction relating to SARS-CoV-2 positive patients. In addition to olfactory dysfunction, SARS-CoV-2 positive patients have also reported symptoms of dysgeusia, which is expected considering gustatory function being highly dependent on olfaction.[24] Several SARS-CoV-2 positive patients reported a solitary gustatory dysfunction, unaccompanied by olfactory dysfunction.[3] Further studies need to be conducted to elucidate if an actual primary gustatory dysfunction exists rather than a consequence of subclinical olfactory dysfunction as suggested by Deems et al.[24]

Proposal for further studies

Olfactory dysfunction is a complex issue, especially PVOD. Despite the various studies discussing PVOD, authors encounter similar obstacles during investigation. Only a few authors have performed studies attempting to isolate viral strains. This is in part because individuals who finally seek medical attention for anosmia present months to years after their viral illness, thinking initially that their olfactory disruption is temporary. By the time patients present, nucleic acid amplification techniques to identify the causative virus can no longer be performed as they are no longer acutely symptomatic from their initial URI. Theoretically, SARS-CoV-2 may be isolated in otherwise asymptomatic, anosmic, SARS-CoV-2 positive patients in the same method by Suzuki et al, Wang et al, or Landis et al.[19—21] Presently, we hesitate to suggest an attempt to isolate SARS-CoV-2 from infected patients unless adequately protected with appropriate personal protective equipment. It has been shown that nasal manipulation, especially endoscopic procedures, routinely performed by otolaryngologists, are highly aerosolizing procedures.[31,32] Currently, multiple otolaryngologic associations are collecting data regarding COVID related anosmia. Although we propose that there is enough existing literature to suggest that COVID-19 related olfactory dysfunction occurs in the same mechanism as the established viral-induced olfactory dysfunction gathered in this review, future studies are needed to confirm our suspicions.

Conclusion

Postviral olfactory dysfunction is a diagnosis with highly complex pathophysiology. Multiple studies have demonstrated similar histologic findings in the olfactory parenchyma in both animal and human subjects that exhibited anosmia following a viral infection. Multiple viruses have been implicated and isolated as the causative agents in patients with PVOD. With the epidemiological evidence that has been presented regarding COVID-19 and olfactory dysfunction thus far, we believe COVID-19 related olfactory dysfunction is likely demonstrating a similar mechanism of what has already been described in the literature regarding PVOD. Further studies, such as histological biopsies of olfactory epithelium and viral isolation of SARS-CoV-2 in infected patients will further solidify our hypothesis.

Conflicts of interest

None of the authors have any conflicts of interest, financial or otherwise.

Financial support

No financial support.

Funding

Not applicable.

Availability of data and materials

The datasets supporting the conclusion of this article are included within the article.

Authors' contributions

SAN, WPL, SAI, PR, RJSdrafted the manuscript;
All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study requires no ethics approval due to public data-based analysis.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication

Not applicable.

Human participants and animal rights

This article does not contain any studies with human participants or animals performed by any of the authors.

Acknowledgements

Not applicable.

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Edited by Yu-Xin Fang