

World Journal of *Clinical Cases*

World J Clin Cases 2022 September 6; 10(25): 8808-9179



Contents

Thrice Monthly Volume 10 Number 25 September 6, 2022

MINIREVIEWS

- 8808** Ear, nose, and throat manifestations of COVID-19 and its vaccines
Al-Ani RM
- 8816** Potential influences of religiosity and religious coping strategies on people with diabetes
Onyishi CN, Eseadi C, Ilechukwu LC, Okoro KN, Okolie CN, Egbule E, Asogwa E

ORIGINAL ARTICLE

Case Control Study

- 8827** Effectiveness of six-step complex decongestive therapy for treating upper limb lymphedema after breast cancer surgery
Zhang HZ, Zhong QL, Zhang HT, Luo QH, Tang HL, Zhang LJ

Retrospective Study

- 8837** Hospital admissions from alcohol-related acute pancreatitis during the COVID-19 pandemic: A single-centre study
Mak WK, Di Mauro D, Pearce E, Karran L, Myintmo A, Duckworth J, Orabi A, Lane R, Holloway S, Manzelli A, Mossadegh S
- 8844** Indocyanine green plasma clearance rate and 99mTc-galactosyl human serum albumin single-photon emission computed tomography evaluated preoperative remnant liver
Iwaki K, Kaihara S, Kita R, Kitamura K, Hashida H, Uryuhara K
- 8854** Arthroscopy with subscapularis upper one-third tenodesis for treatment of recurrent anterior shoulder instability independent of glenoid bone loss
An BJ, Wang FL, Wang YT, Zhao Z, Wang MX, Xing GY
- 8863** Evaluation of the prognostic nutritional index for the prognosis of Chinese patients with high/extremely high-risk prostate cancer after radical prostatectomy
Yang F, Pan M, Nie J, Xiao F, Zhang Y

Observational Study

- 8872** Chlorine poisoning caused by improper mixing of household disinfectants during the COVID-19 pandemic: Case series
Lin GD, Wu JY, Peng XB, Lu XX, Liu ZY, Pan ZG, Qiu ZW, Dong JG
- 8880** Mental health of the Slovak population during COVID-19 pandemic: A cross-sectional survey
Kralova M, Brazinova A, Sivcova V, Izakova L

Prospective Study

- 8893** Arthroscopic anatomical reconstruction of lateral collateral ligaments with ligament advanced reinforcement system artificial ligament for chronic ankle instability
Wang Y, Zhu JX

SYSTEMATIC REVIEWS

- 8906** How to select the quantitative magnetic resonance technique for subjects with fatty liver: A systematic review
Li YW, Jiao Y, Chen N, Gao Q, Chen YK, Zhang YF, Wen QP, Zhang ZM
- 8922** Lymphocytic choriomeningitis virus: An under-recognized congenital teratogen
Ferenc T, Vujica M, Mrzljak A, Vilibic-Cavlek T

CASE REPORT

- 8932** Alagille syndrome associated with total anomalous pulmonary venous connection and severe xanthomas: A case report
Zeng HS, Zhang ZH, Hu Y, Zheng GL, Wang J, Zhang JW, Guo YX
- 8939** Colo-colonic intussusception with post-polypectomy electrocoagulation syndrome: A case report
Moon JY, Lee MR, Yim SK, Ha GW
- 8945** Portal vein gas combined with pneumatosis intestinalis and emphysematous cystitis: A case report and literature review
Hu SF, Liu HB, Hao YY
- 8954** Quadricuspid aortic valve and right ventricular type of myocardial bridging in an asymptomatic middle-aged woman: A case report
Sopek Merkaš I, Lakušić N, Paar MH
- 8962** Treatment of gastric carcinoma with lymphoid stroma by immunotherapy: A case report
Cui YJ, Ren YY, Zhang HZ
- 8968** Gallstone associated celiac trunk thromboembolisms complicated with splenic infarction: A case report
Wu CY, Su CC, Huang HH, Wang YT, Wang CC
- 8974** Extracorporeal membrane oxygenation for lung cancer-related life-threatening hypoxia: A case report
Yoo SS, Lee SY, Choi SH
- 8980** Multi-disciplinary treatment of maxillofacial skeletal deformities by orthognathic surgery combined with periodontal phenotype modification: A case report
Liu JY, Li GF, Tang Y, Yan FH, Tan BC
- 8990** X-linked recessive Kallmann syndrome: A case report
Zhang P, Fu JY
- 8998** Delayed complications of intradural cement leakage after percutaneous vertebroplasty: A case report
Ma QH, Liu GP, Sun Q, Li JG

- 9004** Coexistent Kaposi sarcoma and post-transplant lymphoproliferative disorder in the same lymph nodes after pediatric liver transplantation: A case report
Zhang SH, Chen GY, Zhu ZJ, Wei L, Liu Y, Liu JY
- 9012** Misdiagnosis of pancreatic metastasis from renal cell carcinoma: A case report
Liang XK, Li LJ, He YM, Xu ZF
- 9020** Discoid medial meniscus of both knees: A case report
Zheng ZR, Ma H, Yang F, Yuan L, Wang GD, Zhao XW, Ma LF
- 9028** Simultaneous laparoscopic and arthroscopic excision of a huge juxta-articular ganglionic cyst compressing the sciatic nerve: A case report
Choi WK, Oh JS, Yoon SJ
- 9036** One-stage revision arthroplasty in a patient with ochronotic arthropathy accompanied by joint infection: A case report
Wang XC, Zhang XM, Cai WL, Li Z, Ma C, Liu YH, He QL, Yan TS, Cao XW
- 9044** Bladder paraganglioma after kidney transplantation: A case report
Wang L, Zhang YN, Chen GY
- 9050** Total spinal anesthesia caused by lidocaine during unilateral percutaneous vertebroplasty performed under local anesthesia: A case report
Wang YF, Bian ZY, Li XX, Hu YX, Jiang L
- 9057** Ruptured splenic artery aneurysms in pregnancy and usefulness of endovascular treatment in selective patients: A case report and review of literature
Lee SH, Yang S, Park I, Im YC, Kim GY
- 9064** Gastrointestinal metastasis secondary to invasive lobular carcinoma of the breast: A case report
Li LX, Zhang D, Ma F
- 9071** Post-bulbar duodenal ulcer with anterior perforation with kissing ulcer and duodenocaval fistula: A case report and review of literature
Alzerwi N
- 9078** Modified orthodontic treatment of substitution of canines by first premolars: A case report
Li FF, Li M, Li M, Yang X
- 9087** Renal cell carcinoma presented with a rare case of icteric Stauffer syndrome: A case report
Popov DR, Antonov KA, Atanasova EG, Pentchev CP, Milatchkov LM, Petkova MD, Neykov KG, Nikolov RK
- 9096** Successful resection of a huge retroperitoneal venous hemangioma: A case report
Qin Y, Qiao P, Guan X, Zeng S, Hu XP, Wang B
- 9104** Malignant transformation of biliary adenofibroma combined with benign lymphadenopathy mimicking advanced liver carcinoma: A case report
Wang SC, Chen YY, Cheng F, Wang HY, Wu FS, Teng LS

- 9112** Congenital hepatic cyst: Eleven case reports
Du CX, Lu CG, Li W, Tang WB
- 9121** Endovascular treatment of a ruptured pseudoaneurysm of the internal carotid artery in a patient with nasopharyngeal cancer: A case report
Park JS, Jang HG
- 9127** Varicella-zoster virus meningitis after spinal anesthesia: A case report
Lee YW, Yoo B, Lim YH
- 9132** Chondrosarcoma of the toe: A case report and literature review
Zhou LB, Zhang HC, Dong ZG, Wang CC
- 9142** Tamsulosin-induced life-threatening hypotension in a patient with spinal cord injury: A case report
Lee JY, Lee HS, Park SB, Lee KH
- 9148** CCNO mutation as a cause of primary ciliary dyskinesia: A case report
Zhang YY, Lou Y, Yan H, Tang H
- 9156** Repeated bacteremia and hepatic cyst infection lasting 3 years following pancreatoduodenectomy: A case report
Zhang K, Zhang HL, Guo JQ, Tu CY, Lv XL, Zhu JD
- 9162** Idiopathic cholesterol crystal embolism with atheroembolic renal disease and blue toes syndrome: A case report
Cheng DJ, Li L, Zheng XY, Tang SF
- 9168** Systemic lupus erythematosus with visceral varicella: A case report
Zhao J, Tian M

LETTER TO THE EDITOR

- 9176** Imaging of fibroadenoma: Be careful with imaging follow-up
Ece B, Aydın S

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The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJCC as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The WJCC's CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

September 6, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Ear, nose, and throat manifestations of COVID-19 and its vaccines

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Specialty type:

Otorhinolaryngology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Redaelli de Zinis LO, Italy; Sivanand N, India

A-Editor: Aydin S, Turkey

Received: April 2, 2022

Peer-review started: April 2, 2022

First decision: May 30, 2022

Revised: June 1, 2022

Accepted: July 25, 2022

Article in press: July 25, 2022

Published online: September 6, 2022



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Abstract

Coronavirus disease 2019 (COVID-19) is a highly infectious disease and was designated a pandemic by the World Health Organization (WHO) on March 11, 2020. There are no classical manifestations of the disease. The most prevalent symptoms include fever, cough, dyspnea, myalgia and headache. The main route of transmission of the severe acute respiratory syndrome coronavirus-2 is through the upper respiratory tract. Therefore, it is not strange to find different ear, nose and throat (ENT) symptoms in individuals infected with this virus. Olfactory dysfunction is a common feature of COVID-19; either it is the only presenting symptom or it accompanies other manifestations of the disease. Other otolaryngological features such as sudden sensorineural hearing loss (SSNHL), dysphonia, nasal obstruction, sore throat, *etc.* are less frequent manifestations of COVID-19. These features, in addition, to being presented early in the disease process, certain long-standing symptoms like parosmia, dysphonia, and persistent deafness, are other characteristics of the disease. Geographical variation in otorhinolaryngological prevalence is another problem with this debilitating disease. Local and systemic adverse effects (local site injection pain, fever, myalgia, headache, and others) of the COVID-19 vaccines are more frequent than otolaryngological side effects (anosmia, hyposmia, Bell's palsy, SSNHL, *etc.*). We aimed in this review to summarize the early and persistent ENT symptoms of COVID-19 or after the various COVID-19 vaccines.

Key Words: COVID-19; Otorhinolaryngological features; Otological features; Rhinological features; Laryngological features; COVID-19 vaccines

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Core Tip: The most common otorhinolaryngological manifestations of coronavirus disease 2019 (COVID-19) are olfactory dysfunctions rather than other symptoms (sore throat, nasal obstruction, deafness, dysphonia, tinnitus, *etc.*). They might be present alone or associated with other common features of the disease (fever, cough, myalgia, headache and dyspnea). Adverse effects of the COVID-19 vaccines include local injection pain, fever, myalgia, headache, and others. Otorhinolaryngological side effects like Bell's palsy, anosmia and deafness due to COVID-19 vaccines are reported in the literature as individual cases or small case series. We review the currently available evidence regarding the otorhinolaryngological features of COVID-19 or after vaccination.

Citation: Al-Ani RM. Ear, nose, and throat manifestations of COVID-19 and its vaccines. *World J Clin Cases* 2022; 10(25): 8808-8815

URL: <https://www.wjgnet.com/2307-8960/full/v10/i25/8808.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i25.8808>

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is highly contagious and caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. COVID-19 affects all medical and surgical specialties. Therefore, at the beginning of the COVID-19 pandemic, questions emerged in the mind of ear, nose and throat (ENT) surgeons. First, how can they protect themselves while performing routine tasks in outpatient clinics, wards, and theaters[2,3]. Second, how should they behave with patients who need surgical operations, particularly upper aero-digestive procedures[4]. Lastly, how they can use telemedicine to lessen the burden on health services[5].

COVID-19 has a diversity of presenting features, including classical (fever, cough, fatigue, dyspnea and headache) and nonclassical symptoms like smell and taste abnormalities[6]. It is considered a unique disease because not all affected individuals complain of the same clinical features, as well as long-standing persistence of some of these symptoms in certain patients. Furthermore, the features of the disease vary according to the ethnicity, geographical location, age of the patients, and waves of the disease[7-9].

Otorhinolaryngological symptoms like anosmia, ageusia, dysphonia, deafness, and others might be the only presenting symptom or accompany other features of COVID-19[10]. Patients with these symptoms are screened for the disease by reverse transcriptase polymerase chain reaction of naso- or oropharyngeal swabs to rule out or confirm the disease or quarantine them. Therefore, they play an essential role in controlling the disease[11].

At the beginning of 2021, several vaccines against COVID-19 were approved and given to people to achieve herd immunity to end this pandemic[12]. There is an appearance of certain clinical features, including general and otorhinolaryngological symptoms, following vaccination[13]. We aimed to summarize the various otorhinolaryngological features due to COVID-19 or following vaccination.

CHARACTERISTICS OF SARS-CoV-2

Coronaviruses contain several viruses that infect animals, which may be transmitted to humans and cause acute respiratory illnesses ranging from mild to severe and even critical forms. In 2002 and 2012, two fatal respiratory disease viruses in humans, SARS-CoV-1 and Middle East respiratory syndrome coronavirus, respectively, originated from animals. Therefore, new coronaviruses are considered a major health problem at the beginning of the 21st century[14]. The novel SARS-CoV-2 which emerged in Wuhan, China in December 2019, is a highly infectious virus from a group of coronaviruses. It is the causative agent of COVID-19[1].

Although SARS-CoV-2 is mostly transmitted through droplet or direct contact, transmission through aerosols, urine, mother-to-child, tears, and fecal-oral transmission are other routes[15-19]. The respiratory tract is the part of the body most commonly affected by SARS-CoV-2. However, any organ in the body can be infected by this virus[20]. The specific receptor, angiotensin-converting enzyme (ACE)-2, is distributed in the lungs, vascular endothelial cells, cardiac tissues, kidneys, brain, liver, intestine, pharynx, olfactory epithelium, and other sites and is the targeting receptor of the virus[20].

Similar to other RNA viruses, the novel SARS-CoV-2 has the continuous ability to mutate various genes. As a consequence, these mutating forms enhance the activity of the virus concerning transmissibility and infectivity. An obvious example is the appearance of the delta variant that infected millions of people across the globe[21].

As a result of the emergence of new variants, the Centers for Disease Control and Prevention and the World Health Organization (WHO) have independently developed a classification system for distinguishing various SARS-CoV-2 variants. This system divided these variants into variants of concern (VOCs) and variants of interest (VOIs)[22].

The VOCs are divided into five variants; alpha, beta, gamma, delta and omicron. All of them have mutations in the receptor-binding domain (RBD) and the N-terminal domain (NTD), of which the N501Y mutation located in the RBD is seen commonly in all types except the delta type. This enhances the affinity of the spike protein for the ACE-2 receptors, increasing the viral binding and thereby entrance into the host cells. Two new preprints found that a single mutation of N501Y alone enhances the affinity of the RBD to the ACE-2 receptors about 10-fold more than the ancestral strain (N501-RBD). The binding affinity of both beta and gamma variants with mutations N417/K848/Y501-RBD and ACE-2 receptors was lower than that of N501Y-RBD and ACE-2 receptors. Omicron was rapidly identified as a VOC due to > 30 changes to the spike protein of the virus as well as a sharp increase in the number of cases observed in South Africa. Various mutations were reported; for example A63T in the matrix; T91 in the envelope; Q498R in the RBD of the spike; R203K in the nucleocapsid protein; Y145del in the spike NTD; in addition to many other mutations in the non-structural and spike proteins. As a result, omicron has 13-fold more infectivity of the virus and is 2.8-fold more transmissible than the delta type[22].

VOIs are a group of variants with specific genetic markers that have been linked to changes that may cause increased virulence, inhibition of antibody neutralization as a result of an infection or vaccination, the ability to evade detection, or a decrease in the effectiveness of treatments or vaccination. Currently, the WHO has named eight VOIs, these are epsilon (B.1.427 and B.1.429), lambda (C.37), zeta (P.2), mu (B.1.621), iota (B.1.526), kappa (B.1.617.1), eta (B.1.525), and theta (P.3)[22].

CLINICAL FEATURES OF COVID-19

It is well-known that the most common presenting symptoms of COVID-19 are fever, cough and shortness of breath[23]. However, one of the peculiar characteristics of COVID-19 is that there is no particular symptom that supports its diagnosis and differentiates it from other respiratory infections caused by other viruses.

As a result of the capability of the SARS-CoV-2 to infect the cells in various parts of the body through the ACE-2 receptor, diverse clinical features might be the presenting symptoms, either as an isolated symptom or a combination of complaints. The following, but not exclusively, headache, dizziness, cranial nerve palsy, nausea, vomiting, diarrhea, abdominal pain, and features of renal or heart failure, are manifestations of the disease[24]. Therefore, in the era of COVID-19, every complaint should be taken into consideration to rule out or confirm the diagnosis of this disease to prevent the transmission of the disease and treat the affected people promptly and early.

RHINOLOGICAL FEATURES OF COVID-19

Early research from various countries found that patients with this disease have olfactory and gustatory dysfunctions (OGDs). Therefore the WHO considers these abnormalities as official symptoms of the disease[25].

The possible mechanisms of the olfactory dysfunction include olfactory cleft obstruction, infection of the sustentacular supporting cells, which express ACE-2 receptors, and injury, either in the olfactory sensory cells *via* a neuropilin-1 receptor or the olfactory bulb[26,27]. A study by Xu *et al*[28] reported that the ACE-2 receptors are distributed in the tongue epithelial cells, explaining the possibility of the entrance of the virus through the buccal mucosa. However, an experimental study on a mouse model revealed that there is no such expression of ACE-2 in taste buds, but there is a significant distribution in the basal part of the filiform papillae[29]. Therefore, the possible mechanism of taste dysfunction due to COVID-19 is the direct destruction of the taste receptors due to the viral infection of the epithelial cells with associated inflammation.

OGDs start early during the disease course, either presenting alone or associated with other features of COVID-19. OGDs due to SARS-CoV-2 are more common than other viral causes of upper respiratory tract infections. OGDs are classified into quantitative (hyposmia, hypogeusia, anosmia or ageusia) or qualitative (dysgeusia, parosmia or phantosmia). The majority of these symptoms resolve within a short time, but some might persist for longer, even following the resolution of respiratory manifestations[30]. Of note, from the author's experience, at the beginning of the first wave of COVID-19 in June 2020 in Ramadi City, Iraq, many patients with quantitative OGDs of short duration were seeking advices in public or private clinics. Most of them were resolved spontaneously within a short period (within 2 wk). The first case of parosmia was seen at the end of July 2020 in a 20-year-old woman for 5 mo. This patient acquired COVID-19 on March 1, 2020, in Baghdad City. The number of OGDs decreased in subsequent waves. On the contrary, duration of qualitative OGDs for an average of 6 mo was relatively more frequent. This could be due to either the first variant of the COVID-19 having a greater propensity to

attack the chemosensory regions; people were developing herd immunity from infection of a large population; or COVID-19 vaccination.

Other various rhinological manifestations, such as nasal obstruction, rhinorrhea and sneezing, may be symptoms of COVID-19 but less frequent than OGDs. COVID-19 patients with a history of chronic illness such as diabetes mellitus, hypertension, or cardiac problems are specifically in danger of developing complications such as rhinocerebral mucormycosis[31].

OTOLOGICAL FEATURES OF COVID-19

Several otological manifestations might be a feature of COVID-19 patients, such as sudden sensorineural hearing loss (SSNHL), tinnitus, vertigo, dizziness, otalgia, Bell's palsy, *etc.* They are either single or multiple presenting symptoms and either alone or accompanied by other features of COVID-19[11,32].

A lot of investigations from different geographical areas have reported that dizziness is one of the main manifestations of COVID-19. A prior study from China, reported that dizziness was the main neurological manifestation of the disease[33]. Dizziness is postulated to result from the neuroinvasive nature of SARS-CoV-2. There are five possible mechanisms for SARS-CoV-2 to affect neuronal tissues: the virus reaches the nerve tissues through the blood, which in turn binds with ACE-2 receptors that are present in the capillary endothelium; hypoxia; direct invasion; immune-mediated insult; and hypercoagulopathy[34,35].

Hearing impairment, whether conductive or sensorineural, might be due to COVID-19. Conductive hearing loss is mostly due to Eustachian tube dysfunction. However, direct invasion of the middle ear is another possible cause. Direct invasion of the inner ear results in the initiation of inflammation, which leads to its destruction and superadded infection by microorganisms like bacteria and fungi[11]. This consequence process results in sensorineural deafness. SNHL due to COVID-19 has been reported[11,36,37], but, the causal relationship between its occurrence and the exact pathogenesis is hardly explained owing to two points. First, there was only a low number of studies that presented as case reports or a small number of cases. Second, other studies found that there was no change in the prevalence of the SSNHL between the pre-pandemic and pandemic periods[38]. However, a recent study from Italy found that there was a significantly higher average pure-tone and vestibular involvement in patients with SSNHL in the COVID-19 period in comparison with the pre-pandemic era[38]. Therefore, we recommend further study to explore the role of this disease in the prevalence and mechanisms of SSNHL. Ear problems during this pandemic should be taken into consideration, particularly if they are not associated with other features to rule out or confirm the disease for better prevention and control of the COVID-19.

THROAT FEATURES OF COVID-19

SARS-CoV-2 affects the upper aerodigestive tissues *via* ACE-2 or transmembrane protease/serine subfamily member 2 receptors[39], leading to different manifestations like dysgeusia, sore throat, hoarseness, dysphagia and odynophagia. Moreover, this virus infection can present with acute laryngitis either as acute epiglottitis in adulthood or croup in infants[40,41]. Although COVID-19-induced acute laryngitis is uncommon, being aware of laryngeal difficulties has the following benefits: participation in early disease diagnosis, infection isolation and control, prevention of infection progression, and correct treatment of airway obstruction[40].

A recent multicenter study from Saudi Arabia identified sore throat in 20.9% of the total COVID-19 confirmed cases (1734), ageusia in 11.4% and odynophagia in 9.6%[42]. Sore throat was identified in 153 of 1099 (13.9%) of laboratory-confirmed COVID-19 patients from 552 hospitals in China during the early stages of the pandemic[16]. In 1420 confirmed cases of mild to moderate COVID-19 from 18 European hospitals, taste dysfunction was reported in 54.2%, sore throat in 52.9%, dysphonia in 28.4% and dysphagia in 19.3%[43]. We may conclude from the studies stated above that throat symptoms are common in COVID-19 patients and that the distribution of these manifestations varies geographically. Specific symptoms such as dysphonia and dysphagia may have emerged as a consequence of COVID-19 treatment, particularly in patients who require breathing support[44].

OTORHINOLARYNGOLOGICAL FEATURES FOLLOWING VARIOUS COVID-19 VACCINES

A vaccine is defined as a preparation of biological material that gives an active acquired immunity against a specific infectious agent. This happens by stimulating an immune response to an antigen (molecule of the microorganism)[45]. The first vaccine was developed by Edward Jenner in 1796 against smallpox[46]. Vaccination is the most effective method for long-term prevention and control of any infectious disease. Scientists in various countries since the beginning of the COVID-19 pandemic have

Table 1 Following coronavirus disease 2019 immunizations, some studies observed otorhinolaryngological problems

Ref.	Country	Date	Number of cases	Symptoms	Vaccine
Colella <i>et al</i> [49]	Italy	February 2021	1	Left Bell's palsy	First dose of Pfizer
Repajic <i>et al</i> [50]	United States	February 2021	1	Left Bell's palsy	Second dose of Pfizer
Konstantinidis <i>et al</i> [25]	Greece Germany	May 2021	2	Hyposmia	Second dose of Pfizer
Keir <i>et al</i> [51]	United States	June 2021	1	Phantosmia	Second dose of Pfizer
Lechien <i>et al</i> [52]	France Belgium Italy	September 2021	6	Smell abnormalities ($n = 5$); taste abnormality ($n = 1$)	The first injection of AstraZeneca ($n = 4$); a second injection of Pfizer ($n = 2$)
Wichova <i>et al</i> [53]	United States	October 2021	30	Hearing loss (25), vertigo (5), dizziness (8), tinnitus (15)	Moderna ($n = 18$), Pfizer ($n = 12$)
Jeong and Choi [54]	Korea	December 2021	3	SSNHL	One case after Oxford-AstraZeneca, 2 cases after Pfizer

SSNHL: Sudden sensorineural hearing loss.

mobilized to find effective vaccines to control COVID-19. These efforts have resulted in the development of many vaccines against SARS-CoV-2. The Pfizer COVID-19 vaccine (BNT162b2) was the first vaccine to be approved by the WHO for emergency use on December 31, 2020. Other vaccines were developed later, such as Astra-Zeneca/Oxford COVID-19, Ad26.COV2.S, *etc.*[47].

The COVID-19 vaccines have both local and systemic adverse effects, including headache, fatigue, muscular soreness, malaise, chills, and joint discomfort. Klugar *et al*[48] found that the majority of participating healthcare workers ($n = 599$) experienced at least one of the symptoms listed above. Furthermore, the study found that mRNA-based immunizations had a higher incidence of local adverse effects than viral vector-based immunizations (78.3% *vs* 70.4%; $P = 0.064$). The opposite was true for systemic adverse effects (87.2% *vs* 61%; $P = 0.001$). The majority of these adverse reactions subsided 1-3 d after immunization[48].

Although local and systemic manifestations are common following COVID-19 immunizations, otorhinolaryngological symptoms, such as anosmia, ageusia, SSNHL, Bell's palsy, and others, are rarely documented in the literature (Table 1)[25,49-54].

CONCLUSION

COVID-19 has a wide range of symptoms experienced by those who are infected. Smell and taste abnormalities are the most common ENT symptoms of the disease. They are either the only presenting symptom or associated with other clinical features of COVID-19. Other ENT manifestations such as SSNHL, dysphonia, nasal obstruction, *etc.* are less common than OGDs. COVID-19 is characterized by geographical diversity in symptomatology as well as long-term symptoms. The identification of ENT symptoms is critical in illness prevention and control. The side effects of several COVID-19 vaccinations include anosmia, bell's palsy, SSNHL, tinnitus, and others; however they are less common than the local and systemic signs that occur after vaccination.

FOOTNOTES

Author contributions: Raid M Al-Ani has all contributions, regarding the design of the study, searching for the relevant references, structuring of the manuscript, design of the table, and writing the draft; I read and approved the final draft.

Conflict-of-interest statement: The author declares that there is no conflict of interest.

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S-Editor: Wang DM

L-Editor: Kerr C

P-Editor: Wang DM

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