

**Review Article**

Voice Disorders Associated to Covid-19: A Theory Domain Review

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Abstract

The Corona Virus disease (COVID-19) was detected for the first time in December of 2019, since then many studies reported voice disorders associated with mild and severe COVID-19. These vocal disorders occur from many etiologies, such as neuronal, respiratory, or vocal fold disorders. Also, they can be a consequence of the damage caused by the endotracheal intubation and the inflammatory mediators or even a result of the psychogenic factors, which were explored in this revision. Methods: the method used in this review study was the hybrid-narrative review focusing on theories and hypotheses that could explain the relationship between COVID-19 and voice disorders. Results: the hypotheses found that the most relevant factors that could explain the voice alterations were neurotropic property evidenced on the neuronal route of infection of the Sars-CoV-2, inflammatory factor, endotracheal intubation, pulmonary function, psychogenic factor. Conclusion: the association between COVID-19 and voice disorders seems to be a multifactorial result of mechanical traumas and metabolic alterations caused by the inflammation in COVID. The major elements are trauma by endotracheal intubation, systemic inflammatory repercussion, and direct neuronal damage related to the neurotropism of the virus.

Keywords: COVID-19; Dysphonia; Multifactorial Causalities; Speech-Language Pathology; Voice Disorders

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Citation: Catani GSA, Mocelin AG, Catani ME, Ferreira AJS, Nishimoto GA, et al. (2022) Voice Disorders Associated to Covid-19: A Theory Domain Review. J Otolaryng Head Neck Surg 8: 68.

Received: February 11, 2022; **Accepted:** March 02, 2022; **Published:** March 08, 2022

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Introduction

The Corona Virus Disease (COVID-19) was detected, for the first time, in December 2019, in Wuhan city, China, and further, on March 11, 2020, it was declared by the World Health Organization (WHO) as a “public health emergency of international concern”, as it was already worldwide spread [1]. The human infection with the highly pathogenic coronavirus associated with severe acute respiratory syndrome (SARS-CoV-2) was considered the cause of many infections of the upper and lower respiratory tract infections (RTI) [1].

Among its most common symptoms are fever, fatigue, and dry cough. Less frequently, anorexia, dyspnea, sputum production, and myalgias are reported in more than 25% of the cases. In mild or moderate forms of the disease, it is observed to cause sore throat, rhinorrhea, headaches, nausea, and diarrhea. It is also reported that COVID-19 leads to hyposmia/anosmia and taste disturbances [2]. Despite all of those manifestations in the respiratory tract, it has been described in some studies that COVID-19 can cause vocal disorders such as dysphonia. These vocal disorders can be due to many etiologies, such as neuronal, respiratory, or vocal fold disorders, or even a consequence of the damage caused by the endotracheal intubation and the inflammatory mediators or even of the psychogenic factors, which are going to be explored in this revision.

Production of voice

The voice, as it is heard, is a result of the airstream passing through the vocal folds, making them vibrate and originate the sound of speech, it is resounded and it is articulated in words [3]. Hence, it is exceptional that all of these processes occur reasonably well so the phonation can happen.

To start the phonation, the vocal folds adduct and approximate, reducing or closing the glottis. The expiration muscles contract so the air can flow out the lungs and generate subglottic pressure. As soon as this subglottic pressure overcomes the glottic closing pressure the vocal folds are stimulated into a self-sustained vibration of the superficial layer of the lamina propria along with the epithelial layer. This vocal fold vibration will modulate the airflow into a pulsating jet flow, which further will develop into a turbulent flow in the vocal tract [4]. To make the harmonics, the air vibration is resounded in the pharyngeal, oral, and nasal cavities. To produce the right phonemes and words, the resounded sound will be articulated by the tongue, the upper lip, the lower lip, the upper teeth, the upper gum ridge (alveolar ridge), the hard palate, the velum (soft palate), the uvula (free-hanging end of the soft palate), the pharyngeal wall, and the glottis (space between the vocal cords) [3]. Therefore, any problem in any of these phases will result in a specific and different kind and intensity of dysphonia

Materials and Methods

The method used in this review study is the hybrid-narrative review focusing on theories and hypotheses that could explain the relationship between COVID-19 and voice disorders [5]. One embracing

query was made to research all articles about this topic. The most relevant articles were selected and reviewed. All articles that had been cited as a reference that could explain any relation between COVID and voice disorders were read and reviewed.

Protocol

This review was developed according to recommendations of research from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and according to the hybrid theory domain design of the study.

In this study, the main question was to evaluate what are the existing theories and hypotheses to explain the association between COVID and voice disorder. Being the primary objective “to verify which are the main studied causes of COVID-related voice disorders”.

Research strategy

The authors searched MEDLINE/PubMed, EMBASE, SciELO, and Lilacs databases for all available articles reporting data about the association between COVID and voice disorders. The string used for searching the databases was as follows, considering titles and abstracts: (“covid-19” OR ‘sars-cov-2’ OR ‘severe acute respiratory syndrome’ OR ‘human coronavirus’) AND (‘voice’ OR ‘dysphonia’ OR ‘dyspnea’ OR ‘vocal function’ OR ‘presbyphonia’ OR ‘voice disorder’ OR ‘glottic insufficiency’ OR ‘speech’) AND (‘vagus nerve’ OR ‘vagal fiber’ OR ‘vagal nerve’ OR ‘peripheral nerve’ OR ‘nerve’ OR ‘neurological symptom’ OR ‘axonal transport’ OR ‘neurotropic’).

Study selection

After the studies were searched and listed, the authors evaluated the full texts of eligible articles based on the inclusion and exclusion criteria.

The inclusion criteria were as follows:

1. Article whose main or secondary objective was to identify and/or explore the relation between COVID and voice disorders and/or voice outcomes of COVID.
2. Articles whereof the primary or secondary objective was to investigate mechanisms of infection and/or pathogenicity of Sars-CoV-2 that were linked to voice disorders or vocal cord and vagus nerve injury.

The following types of publications were excluded:

1. Articles that did not investigate any pathophysiological, symptomatic, or subjective outcome that is related to COVID and voice disorder.
2. Articles in a language other than English that does not have full text available in English.
3. Publications where original articles were inaccessible (only abstracts were available) and/or incomplete data were provided.
4. Duplicates.

Collected data

The authors reviewed all relevant studies and independently extracted data. In order to qualitatively compel, the results were explained and summarized the main theory about the association of

COVID and voice disorders available in the medical literature. The results of the review are summarized in the subsequent topics.

Results and Discussion

COVID-19 and Dysphonia

The first studies published didn’t consider dysphonia as one of the clinical symptoms of COVID-19, as it was very overlooked and didn’t catch the attention of the physicians and scientists who were evaluating the sample patients. However, as the researchers were developing and digging deeper, some studies started to consider and question the patients about these problems in the vocal tract, and how it concerned about the voice changes.

A study with European patients with mild-to-moderate forms of COVID-19 showed a dysphonia prevalence of 26,8%, including a range of 3,7% of the patients with aphonia. The severity of dysphonia was significantly associated with the severity of dysphagia. A significant positive association was found between dysphonia and cough [6,7]. In another study, dysphonia was reported in 43,7% of the patients and it was positively associated with voice fatigue, dyspnea, rhinitis, and cough. In those who presented the disorder, it lasted longer than 2 weeks in 47,1% of them and longer than 1 month in 15,7%, showing the importance and the huge impact of this underestimated symptom [8].

Voice disorders are common on viral infections of the upper respiratory tract and can result from several reasons, neuronal infection, inflammation of vocal folds, the deficit of pulmonary function, and complications of ventilatory support with the definitive airway [6,9-11]. Patients with COVID-19 present with significant impairments of voice particularly after prolonged intubations and tracheostomies [9]. Although, mild and moderate cases also present voice disorders, these cases are associated with a significant prevalence (> 40%) of self-evaluated dysphonia among non-hospitalized COVID-19 patients [8].

In this literature review, five main etiological hypotheses were explored to explain the vocal deficits associated with COVID-19.

Neuronal route and infection

Infectious diseases have been associated with an increased risk of neurological manifestations, remarkably in influenza epidemics [12,13]. In the right conditions depending on viral and host factors, all viruses can reach the Central Nerve System (CNS) [14]. Several human respiratory viruses are neuroinvasive and neurotropic, various neurological manifestations have been reported associated with COVID-19, moreover, about one-third of COVID-19 patients present neurological symptoms during the disease including Peripheral Nervous System (PNS) manifestations such as hyposmia, anosmia, ageusia, and muscle pain [15]. The first published case series studies of COVID-19 reported a significant prevalence of neurological manifestations. As with other respiratory viruses, SARS-CoV-2 may infect the central nervous system through the hematogenous or retrograde neuronal route [16,17].

Furthermore, the hypothesis and association of neurological manifestations and neurotropism have been studied since the first cases of COVID-19. Researchers detected SARS-CoV-2 genetic material in cerebrospinal fluid in the autopsy of infected patients, degeneration of some neurons, as well as macroscopic changes in brain tissue as edema, hyperemia [16,18-21]. Besides SARS-CoV-2 presence was

detected in cerebrospinal fluid in a viral encephalitis case and was directly observed in the brain cells of deceased COVID-19 patients, confirming its neurotropic potential [22,23].

Interestingly, vagal neuropathies due to upper respiratory viral infections are already clinically recognized as contributors to various sequelae for infectious and post-infectious [24-26]. Some studies describe that some respiratory viruses can reach the brain by the retrograde route via sensory fibers of the vagus nerve infected by the respiratory tract [20,27,28].

In this scenario, vagus nerve neuropathy rises as an important hypothesis to explain an etiological factor of dysphonia in COVID-19 patients [20]. SARS-CoV-2 seems to follow no specific route into the human host, but several in parallel, going forward in different speeds, which may explain symptom progression. In this case, viral transport along vagus nerve axons is possibly moving about 2 $\mu\text{m}/\text{s}$ in the retrograde direction and because of its anatomy is more likely this dysphonia etiology factor be late [29]. It is known that the vagus nerve function includes the motor, sensory, and taste, involving the pharynx and tongue [30]. The viruses can invade the vagal nucleus and respiratory control center. Therefore, is plausible to hypothesize that if SARS-CoV-2 can reach the brain through the vagus nerve it can lead to respiratory and vocal dysfunction [25,27,28,31].

Inflammatory factor

Infection of SARS-CoV-2 often triggers a phenomenon known as “cytokine storm”, an overproduction of pro-inflammatory cytokines which appears to be greater in severe cases [32,33]. A positive correlation of increased pro-inflammatory factor and severity of COVID-19 cases was described. High levels of IL-2R, IL-6, IL-8, and TNF- α were reported to be higher in COVID-19 patients than in healthy individuals and non-severe cases. In addition, IL-6 has been associated with neuroinflammation mediated by astrocytes and microglia during SARS-CoV-2 infection [34,35]. Curiously, there is evidence of greater levels of IL-6 in the cerebrospinal fluid of patients with COVID-19-associated neurological symptoms [36].

There is evidence that, in viral infections, the acute inflammatory response may also affect nerve conduction, temporarily slowing its function. During the inflammation of the central and peripheral nervous system, cytokines such as interleukins, arachidonic acid, tumor necrosis factor, and viral products released appear to interfere with the electrophysiology properties of neurons [37]. Cytokine's flow was assumed to be one of the main causes of neurological manifestations, such as polyneuropathy, which often accompany the viral damage hypoxia-related in nervus tissues that ultimately associate to the neurotoxic pathway [38,39]. Furthermore, some authors credit to inflammation processes the major contribution portion on dysfunction nerves symptoms such as anosmia [40]. The hypothesis of viral inflammation-causing neuropathy has robust precedents [41].

Viral-induced inflammation is widely believed to have at least three mechanisms whereby viruses may cause neuropathy:

1. direct infection and inflammation,
2. by induction of nonspecific inflammatory response, and
3. nerve injury as a result of the inflammatory cascade as well as Guillain-Barre syndrome pathophysiology is proposed [24,42].

Dysphonia may be associated with laryngeal involvement by the respiratory tract inflammatory process and may be caused by vocal fold edema or inflammation [10]. In addition, the vagus nerve appears that have an important immunomodulatory role in the inflammatory response and inhibition [10,43-45]. Because of that, the vagus nerve infection and damage may contribute to inflammatory factors, which could strengthen the etiology of COVID-19-related dysphonia corditis. However, more studies are necessary to understand the impact of the inflammatory factor in the genesis of COVID-19-related dysphonia.

Endotracheal intubation

Endotracheal intubation (ETT) is part of the treatment protocol for patients with the severe acute respiratory syndrome (SARS) [46]. Since the first outbreak of the COVID-19 epidemic were reported suggestions of healthcare protocols involving endotracheal intubation for severe cases [47,48].

It is known that endotracheal intubation and tracheostomy may cause laryngeal injury, mainly ulcerative lesions that can lead to granuloma formation, vocal fold scarring, and laryngeal stenosis [49-53]. Moreover, functional impact on voice outcomes was a recognized complication of prolonged endotracheal intubation [11,54,55]. Another complication, although uncommon, is the true vocal cord paralysis resulting from peripheral nerve damage caused by nerve compression between an inflated endotracheal tube cuff and the overlying thyroid cartilage [56].

In the COVID-19 pandemic, there were reported increased cases of complications following prolonged intubation and tracheostomy [57]. Hence, tracheal intubation seems to be an important cause of voice disorders COVID-19-related in severe cases. Sequels and short-term effects on voice are associated with endotracheal intubation [58-60]. This cause appears to be the most strongly associated with a vocal deficit in severe cases of COVID-19, however, it does not clarify the voice alterations present in mild and moderate cases that did not require ETT [9]. On the other hand, the direct lesions caused by endotracheal intubation do not explain all about voice alterations on postintubation patients, mainly on short-time intubations. Furthermore, objective measures point out that this speech disorder caused by intubation also is probably multifactorial [61]. Other possible causes to explain vocal fold immobility after prolonged intubation are laryngeal intrinsic muscle myopathy/myositis or arytenoid dislocation and inflammation of the cricoarytenoid joint, despite its lower prevalence could also explain some cases of voice disorders [62,63].

House et al. found that the size of the endotracheal tube and increased duration of intubation ($\mu = 9.7$ days) were not significantly associated with worse laryngeal injury scores. Shinn, however, concludes on a cohort study that an endotracheal tube greater than size 7.0, diabetes, and larger body habitus may predispose to injury [11]. On the other hand, Santos set forth a significant correlation between increasing duration of intubation and degree of laryngeal injury ($\mu = 9$ days). As a consequence, additional studies are required to further elucidate the real impact and mechanism of each variable linked to the patient who needs intubation that can affect the voice.

Pulmonary function

Voice sound production is a complex and delicate process in which the respiratory muscles, lungs, and airflow represent essential factors. Especially subglottal pressure and the glottal airflow are

responsible for the voice production [4,64]. Phonation requires considerable respiratory function in terms of expiratory flow and expiratory excursions in lung volume [65]. Patients with airway obstructions or pulmonary function deficits may experience difficulty sustaining minimum expiratory flow during phonation [66,67]. Thus, dyspnea is a common manifestation in the acute phase of COVID-19 infection but also a persistent symptom and pulmonary damage are important features able to justify voice disorders [68-71]. Since were reported impaired respiratory muscle strength and abnormalities were reported in pulmonary function tests of COVID-19 patients [72]. Thus, it is possible to compare and propose an association between the prevalence of dyspnea and voice changes during and after viral infection. Nevertheless, there may be confounding biases that can be clarified with further future studies.

In addition, surprisingly, the vagus nerve may also be associated with this pulmonary etiology once the upper airway receptors stimulated by the dynamic airway compression distortion and collapse may afford vagal afferent impulses contributing to dyspnea [67,73-75]. However, more researches are necessary to assess the exact significance of this association.

Psychogenic dysphonia

It has been recently established that the SARS-CoV-2 infection may be related to the onset of psychosis, mood disorders, post-traumatic stress depression (PTSD), and even suicide if we consider how self-isolation, physical distancing, and other factors may affect one's mental health [76].

In this matter, such psychological precipitants may also be related to the increase of symptomatology, leading to a special concern over the vulnerability of COVID-19 patients with pre-existent psychiatric conditions, especially those affected by Somatic Syndrome Disorders [77].

Psychogenic dysphonia, by itself, is defined as the onset of voice disorders in the absence of primary organic changes in the larynx [78]. Emotional conditions can directly influence the process of phonation, being connected to the functioning of respiratory, phonatory, and articulation mechanisms of voice production [79].

It is frequently observed in patients between 30 and 50 years of age with emotional dysfunctions, with a mild predominance on the female sex [80]. Those emotional issues may also affect a wide spectrum of aspects, such as vocal intensity, vocal resonance, vocal range, frequency, among others, and it is well established that anxiety, stress, depression, and social problems are important risk factors of this disorder [81].

When it comes to COVID-19, Buseli et al reported a case of a 50-year-old nurse that experienced persistent dysphonia after the resolution of the infection, with no evidence of laryngeal structural dysfunction. Besides the trauma of the disease, this may also be explained by the fact that healthcare professionals are more exposed to moral dilemmas, suffering, and ethical issues, which may contribute to the increase of such symptoms, especially during a worldwide pandemic [79].

Although there is not enough evidence in the scientific literature over COVID-19's impacts on people's mental conditions, it is safe to recognize that traumatic experiences, fear, and insecurity are, in general, strongly related to somatic disorders and increases the experience of symptoms and physical health [82].

Conclusion

The association between COVID-19 and voice disorders seems to be a multifactorial result of mechanical traumas and metabolic alterations caused by the inflammation in COVID. The treatment for COVID can lead to vocal cord trauma when endotracheal intubation is necessary. Furthermore, non-intubated patients might undergo vocal cord trauma because a severe cough can change the voice quality. The mechanical ventilation with endotracheal intubation was found as the most important factor associated with a vocal alteration. Moreover, the neurotropic behavior of Sars-CoV-2 was pointed out as a possible explanation of this association. The role of inflammatory cytokines, the psychogenic hypothesis, and the pulmonary function were evaluated as possible factors that could be involved in the pathophysiology of voice disorder COVID-related. Nonetheless, its impact on voice dysfunction is unclear.

Declaration of Competing Interests

The authors do not have any financial interests or conflicts of interest.

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