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# Bilateral vocal fold paralysis after COVID-19 infection. Another neuro-invasive manifestation? Case series

## *Parálisis bilateral de cuerdas vocales tras infección por COVID-19. ¿Una manifestación neuroinvasiva? Serie de casos*

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### Abstract

The agent that causes the coronavirus disease (COVID-19), associated with the severe acute respiratory syndrome (SARS-CoV-2), produces a spectrum of symptoms that mainly affect the respiratory system, the central nervous system (CNS), the regulation of hemostasis and the immune system. Bilateral vocal fold paralysis (BVFP) is a condition of unknown incidence among infected patients, either because it is short-lived or because of the difficulty in establishing a direct cause to the virus.

Viral infection has been described in the literature as a cause of BVFP and there is the suspicion that a proportion of the idiopathic cases are due to undiagnosed viral infections. Although the neurotropic mechanisms for SARS-CoV-2 remain unclear, there is strong evidence to ensure its neuroinvasive potential. The most frequent etiologies of BVFP are trauma, neoplasm, and neurological, but a viral origin should not be ruled out. Causality between COVID-19 and BVFP is plausible and will require further study in the short and long term. We present a case series that support and discuss the hypothesis under consideration.

**Keywords:** Vocal cords bilateral palsy; Neuroinvasion; Neurotropism; SARS-CoV-2; COVID-19.

### Resumen

El agente causal de la enfermedad por coronavirus (COVID-19), asociado a síndrome respiratorio agudo grave (SARS-CoV-2), genera un espectro de síntomas que afectan fundamentalmente el sistema respiratorio, el sistema nervioso central (SNC), la regulación hemostática y el sistema inmune. La parálisis bilateral de cuerdas vocales (PBCV) es una entidad cuya incidencia en infectados se desconoce, bien porque no se presentan durante el tiempo suficiente o por la dificultad de establecer una causalidad directa con el virus.

La infección vírica, como causa de PBCV, está descrita en la literatura y se sospecha que una parte de los casos idiopáticos corresponden a infecciones víricas no diagnosticadas. Aunque los mecanismos neurotrópicos no están completamente aclarados para el SARS-CoV-2, existen indicios sólidos para asegurar su potencial neuroinvasivo. Las causas traumáticas, neoplásicas y neurológicas son las etiologías más comunes de PBCV, sin que se pueda descartar el origen vírico. Es plausible una causalidad entre el COVID-19 y la PBCV, que requerirá mayores estudios a corto y largo plazo. Presentamos una serie de casos que sostienen y discuten la hipótesis en consideración.

**Palabras clave:** Parálisis bilateral de cuerdas vocales; Neuroinvasión; Neurotropismo; SARS-CoV-2; COVID-19.

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## INTRODUCTION

The agent that causes the coronavirus disease (COVID-19), associated with the severe acute respiratory syndrome (SARS-CoV-2), emerged for the first time in Wuhan (China) in December 2019. It has given rise to a state of emergency among the scientific community, leading to a redefinition of certain principles with regards to infectious diseases, preventive medicine and epidemiology. (1,2)

The progressive knowledge about the spectrum of COVID-19 symptoms has been disseminated gradually and in parallel to the devastating and geographically ubiquitous progression of the pandemic.

Although the pathophysiological mechanisms of the disease are not fully identified, the symptoms affecting the respiratory system as a whole, the mechanisms of homeostasis, the immune system and the central nervous system (CNS) are well known.

There are however a number of disease manifestations of unknown incidence, either because they are too short-lived to be identified, or because of the difficulty in establishing a direct causal relationship to the virus.

The diagnosis, cause and treatment of bilateral vocal fold paralysis (BVFP) are described in the literature. Though many cases of BVFP are classified as idiopathic, there are some viruses able to cause this condition.

This article discusses two clinical cases of COVID-19 patients with BVFP developed after the infection. A causal hypothesis between the clinical presentation and the infection is also submitted as an interesting perspective for future differential diagnoses.

## CASE REPORT

### Case 1

This is a 33-year-old male, type II diabetic treated with oral antidiabetic agents. The

patient was found at home with a low level of consciousness; the airway was secured, and the PCR (polymerase chain reaction) test and IgM serology were positive for SARS-CoV-2 infection. He remained in the intensive care unit (ICU) for 13 days, and required orotracheal intubation (OTI) and mechanical ventilation (MV). The chest X-ray showed bibasilar pulmonary involvement compatible with SARS-CoV-2 infection.

In the ICU the patient underwent electroencephalography and MIR which were normal. A lumbar puncture identified mild cerebrospinal fluid (CSF) pleocytosis and viral encephalitis from the usual viruses was ruled out.

The patient had been admitted to the emergency department 27 days before discharge, with unresponsive dyspnea and stridor for the last few hours. The chest X-ray showed an interstitial pattern probably associated with COVID-19. An indirect fiber optic endoscopy revealed adduction of the vocal folds with significant narrowing of the glottic space, so the patient was transferred to the operating room for urgent airway control.

At admission to the OR, the patient presented with acute dyspnea, tachypnea, 90% oxygen saturation and stridor. OTI was performed under videolaryngoscopy, and as classified as modified Cormack 1, with complete adduction of the vocal folds.

The patient adapted well to the MV. After the surgical review, the decision was to continue with watchful waiting without

tracheostomy in the ICU. The patient was maintained intubated with sedation/analgesia, stable and methylprednisolone treatment 1 mg/kg/24h was initiated.

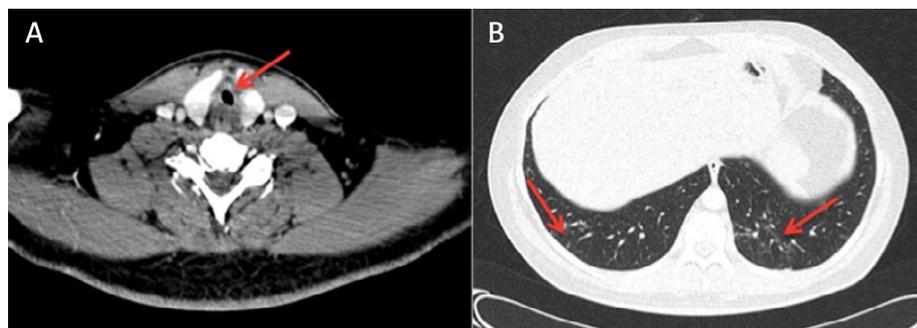
The patient was extubated after 48 hours under fibrobronchoscopy control, observing mild bilateral vocal fold paresis, with sufficient glottic space. Since the patient was eupneic and with mild dysphonia, he was transferred from the ICU to the hospital ward and was subsequently discharged.

72 hours later the patient was readmitted with an episode of dyspnea and stridor. A CT-scan showed stenosis of the subglottic short axis 15 mm from the glottis, with a 5mm lumen, suggestive of postintubation injury (Image 1a) and bibasilar pulmonary involvement with less than 10% fibrosis (Image 1b). The patient underwent urgent tracheostomy and was scheduled for fibrobronchoscopy-guided tracheal balloon dilatation. The procedure achieved an adequate lumen and subsequent uneventful decannulation.

### Case 2

This is a 60-year-old male, hypertensive with enalapril treatment, who was admitted one month earlier with a diagnosis of bilateral interstitial pneumonia due to SARS-CoV-2. The patient stayed 27 days in the ICU requiring invasive respiratory support. In the ICU he was treated with methylprednisolone at a dose of 1 mg/

**IMAGE 1.** TCT scan. A. Short axis subglottic stenosis. B. Pulmonary involvement.



**SOURCE.** Authors.

kg/24h and developed complications including bacteremia secondary to *Enterococcus faecalis* which was treated with ampicillin, and a tracheobronchitis secondary to methicillin-susceptible *Staphylococcus aureus* which was treated with cloxacillin.

40 days after hospital discharge, the patient returned to the emergency department with foreign body sensation, dyspnea and tachycardia, in addition to inspiratory stridor and asthenic voice. The fibrolaryngoscopic examination evidenced a paramedial vocal fold position, with minimum space for air passage (*Image 2a*). The patient was diagnosed with BVFP and underwent urgent tracheostomy under local anesthesia.

Additional tests included PCR (negative) and serology (IgM and IgG were positive) for SARS-CoV-2. The head and neck CT were normal and the chest X-ray evidenced a pattern compatible with past COVID-19 pneumonia (*Image 2b*).

The patient was discharged with indication of ENT follow-up visits for the BVFP and the tracheostomy.

## DISCUSSION

BVFP is characterized by immobility of the vocal folds in adduction or complete abduction, or in paramedial position. (3) The term refers to the absence or decreased function of the vagus nerve, at any point of

its terminal branch along the recurrent laryngeal nerve. (3-7) It is considered a rare disorder, representing one third of the total vocal fold paralyses. (7) Similar to other vocal fold diseases, BVFP has a higher female prevalence as compared to males. (5)

The clinical manifestations of BVFP have variable levels of stridor and dyspnea. (3-7) The complete obstruction of the airway lumen is an indication for and urgent tracheostomy approach. (3)

The diagnosis of BVFP is done clinically through indirect fibrolaryngoscopy and strobe light. (5,6) The differential diagnosis is based on the medical record, the laryngoscopy findings and the laryngeal electromyography. (5)

The most frequent etiology in BVFP is trauma after thyroid surgery, followed by neoplasms and neurological disorders. (3-6,8) Idiopathic paralyses range between 0.6-50 % of the cases. (6)

The viral hypothesis of BVFP has been described as secondary to influenza A, Epstein-Barr, cytomegalovirus, herpes simplex or varicella zoster. (8-10) It is thought that a significant proportion of the idiopathic cases correspond to undiagnosed viral infections. (11)

Paralyses secondary to viral infections exhibit a good prognosis with complete resolution in most patients, but early pharmacological therapy is important when the causal agent has been identified. (8-10)

In paralyses with high suspicion of viral infection, imaging tests shall be conducted, in addition to a neurological examination, a lumbar puncture for CSF analysis and PCR to rule out encephalitis of the most common viruses, as well as serological testing for these most frequent viruses. (8,9)

The mechanism whereby most of the viruses described may cause a BVFP is through reactivation that allows the virus to migrate through the nerves to the skin and other organs such as the CNS, causing cranial nerve paralysis, among other disorders. (8-10)

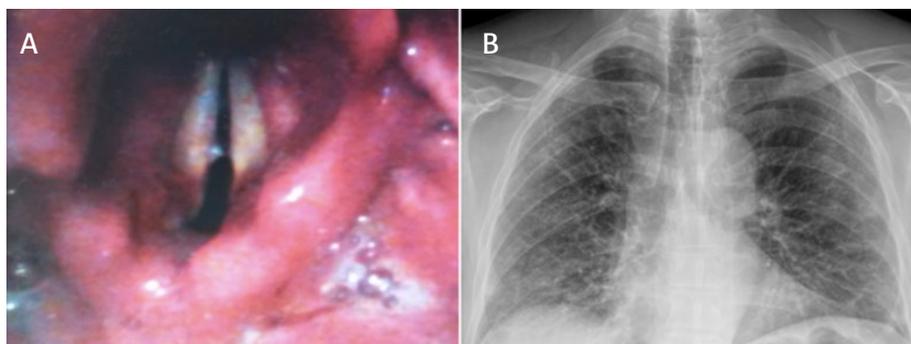
Some viruses can be neurotropic and capable of invading the different cells in the CNS, with the potential to develop various types of encephalitis and intracranial infections. (12) Some coronaviruses (CoV) have shown their neuroinvasive potential, because they become isolated in the CSF—i.e., they enter the CSF— which further supports the theory of their potential involvement with nerve tissue injury. (12-14) It's been estimated that 24.8 % of SARS-CoV-2 infected patients develop central neurological symptoms, with 10.7 % affecting the peripheral nervous system. (12-15)

Neurological symptoms have been described in patients with COVID-19, including headache, myalgia and anosmia, encephalopathy, hemorrhagic necrotizing encephalitis, stroke, epileptic seizures, rhabdomyolysis and Guillain-Barré syndrome (GBS), associated with SARS-CoV-2 infection. (15) With regards to GBS, a strong link has been shown between both conditions, though there are differences in the presentation of both diseases, with a higher severity of the conditions associated with COVID-19. (16)

The pathophysiological mechanisms suggested for CNS-CoV-associated injury are: direct infection injury, hypoxic lesion, immune lesion and angiotensin converting enzyme (ACE II) receptor interaction. (12)

In case of direct invasion, bloodstream dissemination (where CoV does not play a preponderant role), and neuronal migration (with a typical olfactory pathway dissemination, through the cribriform plate of the ethmoid bone) are the most relevant

**IMAGE 2.** A. Fibrolaryngoscopy. B. Chest X-ray.



**SOURCE.** Authors.

during the early stages of the infection, with the virus entering the nerve tissue. (12-14)

In the case of a hypoxic lesion, the SARS-CoV-2-associated lung injury produces a gas exchange dysfunction and CNS hypoxia leading to acidosis, cerebral vasodilatation, inflammation of the brain cells, interstitial edema, cerebral blood flow obstruction and even headache due to ischemia and congestion. (12)

In immune lesion, the ability of the SARS-CoV to inflict severe pneumonia and a systemic inflammatory response syndrome facilitates the persistence of infection, allowing the virus to contaminate macrophages, glial cells and astrocytes and favoring a proinflammatory status which further aggravates via a cytokines cascade (IL6, IL-12, IL-15 y TNF- $\alpha$ ). (12,13)

ACE II expresses largely in the epithelial cells of the lung, the cardiac myocytes, and the vascular endothelial cells. (17) ACE II receptors represent a target for SARS-CoV-2 mediating their cell invasion. Moreover, the virus negatively regulates the ACE II expression which converts angiotensin I and II into cardioprotective peptides, so its loss on the cellular surface may aggravate cardiac injury. (17) Decreased ACE II on the vascular endothelium may exacerbate the endothelial dysfunction, inflammation and thrombosis, in addition to damaging the blood-brain barrier and lead to vascular CNS invasion. (12,13,17)

ACE II expression in the vascular endothelial cells is associated with the underlying pathological condition, age and gender. Its activity is decreased in the vessels with established atherosclerotic plaque and diabetes. Hypertension is frequently identified in patients with COVID-19, but it is unclear whether it is a risk factor to develop the infection. (17)

Establishing a causality between these two clinical cases and BVFP is complex, since it is impossible to rule out other etiological causes, and we must not forget that a large proportion of BVFPs are idiopathic. Based on the viral hypothesis, SARS-CoV-2 could lead to a direct invasion via neuronal

migration which in turn could affect the cranial nerve involved in the paralysis.

BCFP is a rare condition, and its more frequent clinical manifestations include dyspnea, shortness of breath and stridor. The approach to BVFP may involve an emergency situation requiring urgent airway management.

Knowledge about the secondary complications of SARS-CoV-2 may contribute with valuable information that facilitates clinical management and provides patient safety.

While waiting for studies in larger populations and a complete understanding of the neuroinvasive mechanisms of the virus, SARS-CoV-2 infection should be considered in the differential diagnosis of BVFP.

## ETHICAL RESPONSIBILITIES

### Protection of animals and humans

No experiments were conducted in humans or in animals.

### Right to privacy and informed consent

The authors obtained the authorization and informed consent from the patients. It rest in the custody of the authors of this article.

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### Contribution by the authors

**JJCB:** Conducted the research, collected the information and drafted the manuscript.

**BGPV, PSZ, AOV, NMG, SSS, MSJA, RSC, DOV, AGR:** Drafting of the manuscript and collected data.

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None declared.

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## Conflict of interests

None declared.

## Presentations

None declared.

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