Overcoming Neuromuscular Sequelae After Severe SARS-CoV-2 Infection: A Case Report

Superação de Sequelas Neuromusculares Após Infeção Grave por SARS-CoV-2: Relato de um Caso

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Resumo

Sintomas neurológicos podem ocorrer em até 65% dos casos de COVID-19. Este artigo pretende alertar para essa afeção neurológica. Descrevemos o caso de um homem de 52 anos, que necessitou de intubação e ventilação mecânica devido a infeção grave por SARS-CoV-2 com síndrome de dificuldade respiratória aguda. Após extubação, apresentava tetraparesia, com membro superior direito plégico, fraqueza global do membro superior esquerdo e fraqueza proximal sem ativação muscular distal nos membros inferiores. Os reflexos osteotendinosos apresentavam-se diminuídos ou ausentes. Verificava-se também hipostesia tátil e álgica do membro superior direito e hiperestesia distalmente nos membros inferiores. Após investigação extensa, foi diagnosticada fraqueza muscular adquirida nos cuidados intensivos e lesão do plexo braquial direito. O doente foi integrado num programa de reabilitação, registando-se melhoria lenta mas progressiva. Na reavaliação após um ano, era capaz de realizar marcha autónoma com ortóteses tipo *foot-up* bilateralmente e necessitava de tripé para superfícies instáveis, mantendo o membro superior direito afuncional. Este artigo descreve várias sequelas neurológicas verificadas num doente com infeção grave por SARS-CoV-2 após internamento em Unidade de Cuidados Intensivos. O envolvimento neurológico associado à infeção por SARS-CoV-2 e respetiva abordagem terapêutica deve ser considerado precocemente pelas equipas médicas e deverão ser oferecidos cuidados de reabilitação.

Palavras-chave: COVID-19/complicações; Fraqueza Muscular/reabilitação; Manifestações Neurológicas/reabilitação; SARS-CoV-2; Síndrome Pós-COVID-19 Aguda

Abstract

Neurologic symptoms can occur in up to 65% of COVID-19 cases. This article aims to raise awareness to such neurologic impairments. We describe the case of a 52-year-old patient who required intubation and mechanical ventilation due to severe SARS-CoV-2 infection with acute respiratory distress syndrome. After extubation, he presented tetraparesis, with plegic right upper limb, global weakness of the left upper limb, and lower limb proximal weakness without distal muscle activation. Deep tendon reflexes were either decreased or absent. Right upper limb tactile and algic hypoesthesia and distal hyperesthesia in both lower limbs were also noticed. Following extensive investigation, intensive care unit-acquired weakness and right brachial plexus injury were diagnosed. He was engaged in a rehabilitation program and showed slow yet progressive improvement. At one-year follow-up evaluation, he was capable of performing independent gait with bilateral foot-up orthosis and used a tripod for unstable floorings, but maintained a non-functional right upper limb. This article describes multiple neurologic sequelae seen in a patient with severe SARS-CoV-2 infection after Intensive Care Unit hospitalization. Neurologic involvement associated to SARS-CoV-2 infection and its respective therapeutic management

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must be taken into account early on by medical teams and rehabilitation care should be offered.
Keywords: *COVID-19/complications; Muscle Weakness/rehabilitation; Neurologic Manifestations/rehabilitation; Post-Acute COVID-19 Syndrome; SARS-CoV-2*

Introduction

In December 2019, the first cases of an unknown etiology pneumonia were reported in China.[1] In January 2020, these were attributed to a novel coronavirus responsible for severe acute respiratory syndromes (SARS) and therefore named SARS-CoV-2.[2] The disease caused by this virus has since been called COVID-19.[1]

SARS-CoV-2 is a positive-sense single-stranded RNA virus from the *Coronaviridae* family.[1,2] Infection with this pathogen can range from asymptomatic to multiple organ dysfunction. It is reported to enter human cells through angiotensin-converting enzyme (ACE) 2 receptors expressed in type II alveolar epithelial cells, justifying its respiratory predilection.[1,2]

As for neurologic affection, reports suggest it can happen due to direct viral action via ACE 2 receptors in specific areas of the brain and spinal cord, or by systemic inflammation, thromboembolism, or endothelial dysfunction.[2,3] Different studies report neurologic symptoms in up to 65% of COVID-19 patients and these impairments appear to be greater in cases of severe disease.[2-4] Neurologic signs and symptoms of COVID-19 include anosmia, ageusia, headache, dizziness, encephalopathy/encephalitis, acute cerebrovascular events, seizures, cranial nerves palsy or neuritis, movement disorders, acute myelitis, Guillain-Barré syndrome (GBS), and dysautonomia.[3-6] COVID-19-related peripheral neuropathies other than GBS have been less frequently reported, with one study mentioning peripheral nerve injuries in 14.5% of patients.[7]

This report aims to raise awareness to neurologic impairments associated to SARS-CoV-2 infection and its therapeutic management, by describing the case of a patient who developed peripheral nervous system sequelae following severe SARS-CoV-2 infection and ICU hospitalization.

A brief description of the case portrayed in this article was presented as a poster at the Virtual ISPRM Congress on June 12th-15th, 2021.

Case Report

We present the case of a previously independent 52-year-old male who worked as janitor at a school. Relevant medical history included metabolic syndrome, a known risk factor for severe SARS-CoV-2 infection.[8]

He was admitted to the emergency room (ER) on March 26th, 2020, complaining of aggravated dry cough with onset in the prior two weeks, associated with anosmia and a maximum temperature of 38ºC. He denied dyspnea, nausea or vomiting, recent travels, and contact with confirmed COVID-19 cases. At admission, he was conscious and oriented, febrile but hemodynamically stable, and tachypneic, presenting peripheral oxygen saturation of 88% in ambient air. Pulmonary auscultation revealed diffuse wheezing and rhonchi. Arterial blood gas testing performed after oxygen supplementation demonstrated hypoxemic respiratory failure and respiratory alkalosis. Blood tests revealed leukocytosis and elevated C-reactive protein. Chest X-ray in posteroanterior projection showed diffuse bilateral infiltrates, raising suspicion of SARS-CoV-2 infection, later confirmed via RT-PCR testing of nasopharyngeal secretions.

During ER stay, the patient presented rapid clinical deterioration meeting criteria for moderate acute respiratory distress syndrome (ARDS), ending up being transferred to the Intensive Care Unit (ICU) and subject to orotracheal intubation. He was extubated 21 days later, after one failed attempt. Additionally, because of suspected bacterial superinfection, a cycle of flucloxacillin and vancomycin was completed, with progressive improvement of blood gas exchange. Following extubation, in mid-April 2020, the patient presented flaccid tetraparesis, with clear asymmetry between the upper limbs. Computed tomography (CT) scans of the head and cervical spine excluded acute central lesions. He also presented episodes of atrial fibrillation, having been submitted to electrical cardioversion and hypocoagulated accordingly.

Considering the patient's cardiorespiratory improvement, he was transferred to a regular COVID-19 ward after 25 days in the ICU. He was later diagnosed with low-intermediate risk pulmonary thromboembolism, motivating hypocoagulation dose increase and further prophylaxis with elastic compression stockings. Due to initial pandemic restrictions of access to the ICU, assessment by the Physical Medicine and Rehabilitation (PMR) team was only requested at this point. On evaluation, the patient presented a plegic right upper limb (RUL), global weakness of the left upper limb (LUL) (Medical Research Council, MRC, grade 3), and lower limb proximal weakness without distal muscle activation, grading MRC 2 in hip flexion and 3 in knee

extension bilaterally. His MRC Sum Score (MRC-SS) was 19/60, rendering him severely dependent. All deep tendon reflexes of the RUL and the Achilles reflex bilaterally were absent. The LUL reflexes, as well as the patellar reflex bilaterally, were decreased. Tactile and algic hypoesthesia in all territories of the RUL and symmetrical distal hyperesthesia in both lower limbs were also noticed. There were no speech or swallowing impairments after extubation and skin integrity was preserved. The patient was prescribed global and respiratory physiotherapy.

He was transferred to the PMR ward on May 18th, 2020, to continue an intensive daily rehabilitation program also including occupational therapy and rehabilitation nursing care. Psychological support was also offered. At admission, he maintained the aforementioned deficits and needed maximal assistance in feeding, grooming and dressing, and total assistance in bathing. He had very poor bed mobility, needed a hoist for transfers and used a wheelchair propelled by third person for ambulation, scoring 60/126 points in the Functional Independence Measure (FIM) scale (motor score: 25/91; cognitive score: 35/35).

Further etiological investigation with electromyography (EMG) was conducted. The first EMG, held in May 2020, revealed extensive fibrillation potentials in multiple RUL myotomes, suggestive of severe acute axonal injury of the right brachial plexus. Brachial plexus magnetic resonance imaging (MRI) revealed hypersignal of the plexus' components as well as of adjacent muscle structures. EMG also demonstrated early recruitment and polyphasic myopathic potentials in the proximal muscles of the LUL, as well as absent voluntary activity distally in the lower limbs and slightly decreased motor unit recruitment proximally. A follow-up EMG was performed in September 2020, confirming the previous results. These findings combined led to the diagnosis of severe intensive care unit-acquired weakness (ICUAW) and right brachial plexus injury.

The rehabilitation process was constrained early on by the presence of an abscessed hematoma of the gluteal region, originating spontaneously in a hypocoagulated patient. This hematoma motivated relative bed rest for about two months, requiring multiple cycles of antibiotics and surgical drainages. Nonetheless, after this problem was resolved, the patient showed excellent adhesion to the rehabilitation program, with slow yet progressive motor and functional improvement over time. In October 2020, his MRC-SS was 32/60 and the total FIM score was 97/126. He had significantly better bed mobility and was already capable of sitting independently and standing with the aid of a tripod, with satisfactory balance. He was under gait training with bilateral foot-up orthosis, assisted by third person. He was therefore discharged from the acute care hospital and transferred to a rehabilitation center to engage in a multimodal and intensive rehabilitation program focusing in achieving independence in activities of daily living (ADL) and gait. He was then discharged from inpatient care after three months, in January 2021, maintaining ambulatory rehabilitation. His MRC-SS at this point was 36/60; the RUL scored 1 (MRC) for shoulder abduction and all finger movements, and 3 for elbow and wrist extension; the LUL had grade 4 muscle strength globally; the lower limbs scored grade 4 in hip flexion and knee flexion and extension, and maintained grade 0 in the distal segments. The patient achieved significant improvement in functionality, scoring a total of 109/126 points in the FIM scale. He had modified independence in all ADL, taking longer to complete them, performing them while seated, or using assistive devices. He was capable of walking for short distances with a tripod and bilateral foot-up orthosis (Fig. 1), with decreased step length and a tendency to external rotation of the lower limbs, in order to improve balance.

Figure 1 - Patient's gait pattern with bilateral foot-up orthosis and tripod.

In the follow-up appointment, one year after the diagnosis (March 2021), the patient maintained ambulatory rehabilitation and was capable of independent gait with the orthosis, using the tripod for unstable floorings. He

maintained modified independence in all ADL. Despite being able to partially move some segments, he maintains a non-functional RUL and wears a shoulder sling while walking. As the patient was right-handed, he is currently transferring hand laterality successfully, being already capable of writing with his left hand. Nowadays, he has returned to work at the same school, changing his activity to the reception desk.

A summary of the patient's clinical information and a timeline of events are depicted in Table 1 and Fig. 2, respectively.

Table 1 - Patient's clinical information.

Patient's clinical information	
Age	52
Gender	Male
Medical history	High blood pressure; Type 2 diabetes *mellitus*; Dyslipidemia; Obesity (grade 3, BMI 42 kg/m^2)
ICU stay (days)	25
Intubation and invasive ventilation	Yes
Corticotherapy	Yes
ICUAW	Yes (Flaccid tetraparesis)
ICU-Acquired swallowing disorder	No (FOIS 7)
Speech impairments	No
Peripheral nerve injury (site)	Right brachial plexus
MRC-SS	After extubation: 19/60
	After 7 months: 32/60
	After 10 months: 36/60
	After 12 months: 37/60

BMI, body mass index; ICU, Intensive Care Unit; ICUAW, intensive care unit-acquired weakness; FOIS, Functional Oral Intake Scale; MRC-SS, Medical Research Council Sum Score.

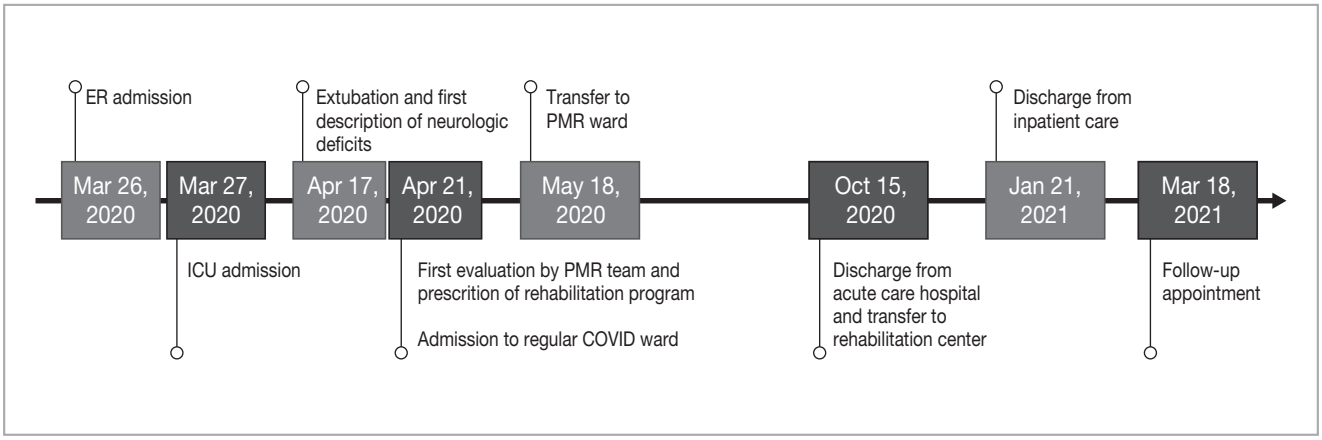

Figure 2 - Timeline of events from Emergency room admission to the one-year follow-up appointment.

ER, Emergency room; ICU, Intensive Care Unit; PMR, Physical Medicine and Rehabilitation.

Discussion

SARS-CoV-2 appears to have neurotropism, causing central and peripheral neurologic manifestations, similarly to other coronaviruses.[9] Several theories have been proposed to explain this involvement, including direct nervous system invasion, hematogenous pathways, peripheral nerve viral entry facilitation, severe immune system reactions to SARS-CoV-2, systemic inflammatory response syndrome, and cytokine storm.[2,3,10]

This case report describes multiple neurologic sequelae seen in a patient with severe SARS-CoV-2 infection after ICU hospitalization, namely ICUAW and brachial plexus injury.

Peripheral nerve injuries during ICU stay have been reported as a neuromuscular complication of COVID-19.[11] COVID-19 patients in ICU may be more susceptible to this complication due to prolonged immobilization and prone positioning,[11] causing compression and stretching of nerves.[7,11,12] As COVID-19 continues, more cases with neurologic sequelae following infection are being reported.

ICUAW is a neuromuscular disorder seen in approximately 25%-45% of critically ill patients, characterized by generalized muscle weakness and failure to wean from the ventilator.[11] This clinical entity is associated with increased mechanical ventilation periods and mortality, and poor functional outcomes in post-ICU patients.[11]

To date, no distinctive features have been reported in COVID-19-related ICUAW regarding clinical findings,[11] such as patient background, symptoms, and electrophysiological studies.[11,13,14] This patient presented known features and risk factors for ICUAW including the presence of ARDS (requiring prolonged mechanical ventilation) and the use of corticotherapy.[15] Furthermore, EMG confirmed the presence of axonal sensorimotor neuropathy with a myopathic element.

Evidence regarding long-term functional outcomes in COVID-19-related ICUAW is still being studied.[11] It is known that non-COVID-19 patients with ICUAW can suffer long-term effects, as functional status and quality of life can be affected from months to years.[11,16] These effects have also been reported in COVID-19-related ICUAW.[16]

As mentioned above, peripheral nerve injuries associated with ICU stay have also been reported as possible complications in severe COVID-19 cases.[11,12] In these cases, prolonged deep sedation and immobilization could increase the chance of peripheral nerves injuries.[10] Additionally, lack of appropriate positioning and sustained proning can cause compression or stretching on nerves and plexuses.[11,12] According to different reports, the incidence of peripheral nerve injuries among COVID-19 patients who underwent ICU hospitalization is 14.5%-16%,[7,11] and the main sites involved are the brachial plexus, median nerve, ulnar nerve, radial nerve, sciatic nerve, and fibular nerve.[7,10,11]

The presented patient has a similar background to previously reported cases;[11,12,14,17] he required prolonged invasive ventilation and was prone positioned during ICU stay. It is known that this position can cause brachial plexus injury due to upper limb extension accompanied by excessive nerve stretching,[11] as observed in our case. As such, we hypothesize that these factors, along with extended ICU stay, may have contributed to the development of ICUAW and peripheral nerve injury in this patient.

A multiprofessional and interdisciplinary rehabilitation program was introduced. However, non-functional RUL persisted after one year, influencing overall functionality, albeit ICUAW-related muscle weakness improved significantly. Proper preventive strategies for these impairments such as frequent mobilization and positioning precautions should be taken and are essential to improve functional outcomes.

To conclude, SARS-CoV-2 has the potential for multisystemic manifestations. Neurologic involvement associated to SARS-CoV-2 infection and its respective therapeutic management must be taken into account early on by medical teams and rehabilitation care should be offered. We expect this report to provide support for the assessment of long-term prognosis in similar cases.

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Referências / *References*

1. Li X, Zai J, Zhao Q, Nie Q, Li Y, Foley BT, et al. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. J Med Virol. 2020;92:602-11. doi: 10.1002/jmv.25731.
2. Kase Y, Okano H. Neurological pathogenesis of SARS-CoV-2 (COVID-19): from virological features to clinical symptoms. Inflamm Regen. 2021;41:15. doi: 10.1186/s41232-021-00165-8.
3. Solomon T. Neurological infection with SARS-CoV-2 – the story so far. Nat Rev Neurol. 2021;17:65-6. doi: 10.1038/s41582-020-00453-w.
4. Carlos CR, Gerardo MM, Jaime OG, Isauro GHL, Dios APJ, Neurosurgical Group. Prevalence of neurological manifestations in COVID-19 and their association with mortality. Neurology Perspectives. 2021;1:11-6. doi: 10.1016/j.neurop.2021.03.002.
5. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen A, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology. 2020;95:e1060-70. doi: 10.1212/WNL.0000000000009937.
6. Sharifian-dorche M, Huot P, Osherov M, Wen D, Saveriano A, Giacomini PS, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. J Neurol Sci. 2020;417:117085. doi: 10.1016/j.jns.2020.117085.
7. Malik GR, Wolfe AR, Soriano R, Rydberg L, Wolfe LF, Deshmukh S, et al. Injury-prone: peripheral nerve injuries associated with prone positioning for COVID-19-related acute respiratory distress syndrome. Br J Anaesth. 2020;125: e478-80. doi: 10.1016/j.bja.2020.08.045.
8. Makhoul E, Aklinski JL, Miller J, Leonard C, Backer S, Kahar P, et al. A review of COVID-19 in relation to metabolic syndrome: obesity, hypertension, diabetes, and dyslipidemia. Cureus. 2022;14: e27438. doi:10.7759/cureus.27438.
9. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11:995-8. doi: 10.1021/acschemneuro.0c00122.
10. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses. 2020;12:14. doi: 10.3390/v12010014.
11. Hokkoku K, Erra C, Cuccagna C, Coraci D, Gatto DM, Glorioso D, et al. Intensive care unit-acquired weakness and positioning-related peripheral nerve injuries in COVID-19: a case series of three patients and the latest literature review. Brain Sci. 2021;11:1177. doi: 10.3390/brainsci11091177.
12. Nasuelli NA, Pettinaroli R, Godi L, Savoini C, De Marchi F, Mazzini L, et al. Critical illness neuro-myopathy (CINM) and focal amyotrophy in intensive care unit (ICU) patients with SARS-CoV-2: a case series. Neurol Sci. 2021;42:1119-21. doi: 10.1007/s10072-020-04820-9.
13. Cabañes-martínez L, Villadóniga M, González-rodríguez L, Araque L, Díaz-Cid A, Ruz-Caracuel I, et al. Neuromuscular involvement in COVID-19 critically ill patients. Clin Neurophysiol. 2020;131:2809-16. doi: 10.1016/j.clinph.2020.09.017.
14. Bagnato S, Boccagni C, Marino G, Prestandrea C, D'Agostino T, Rubino F. Critical illness myopathy after COVID-19. Int J Infect Dis. 2020;99:276-8. doi: 10.1016/j.ijid.2020.07.072.
15. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care. 2015;19:274. doi: 10.1186/s13054-015-0993-7.
16. Sidiras G, Patsaki I, Karatzanos E, Dakoutrou M, Kouvarakos A, Mitsiou G, et al. Long term follow-up of quality of life and functional ability in patients with ICU acquired weakness – A post hoc analysis. J Crit Care. 2019;53:223-30. doi: 10.1016/j.jcrc.2019.06.022.
17. Van Aerde N, Van den Berghe G, Wilmer A, Gosselink R, Hermans G, COVID-19 Consortium. Intensive care unit acquired muscle weakness in COVID-19 patients. Intensive Care Med. 2020;46:2083-5. doi: 10.1007/s00134-020-06244-7.