IMPACTS OF COVID-19 ON THE IMMUNE, NEUROMUSCULAR, AND MUSCULOSKELETAL SYSTEMS AND REHABILITATION

IMPACTOS DA COVID-19 NOS SISTEMAS IMUNOLÓGICO, NEUROMUSCULAR, MUSCULOESQUELÉTICO E A REABILITAÇÃO

IMPACTOS DE LA COVID-19 EN LOS SISTEMAS INMUNITARIO, NEUROMUSCULAR, MUSCULOESQUELÉTICO Y LA REHABILITACIÓN

Special article
Artigo especial
Articulo especial

Júlia Maria D'Andréa Greve[1] (Physician)
Guilherme Carlos Brech[1,2] (Physiotherapist)
Marília Quintana[2,3] (Physiotherapist)
André Luiz de Seixas Soares[1] (Physiotherapist)
Angelica Castilho Alonso[1,2,3] (Physiotherapist)

1. Universidade de São Paulo, Faculdade de Medicina, Orthopedics and Traumatology Department, Laboratory for Studies in Movement - São Paulo, SP, Brazil.
2. Postgraduate Program in Sciences of Aging of Universidade São Judas Tadeu, São Paulo, SP, Brazil.
3. Universidade Anhembi Morumbi, São Paulo, SP, Brazil.

Correspondência
Júlia Maria D'Andréa Greve. Instituto de Ortopedia e Traumatologia do Hospital das Clínicas – Laboratory for Studies in Movement (LEM). Rua Ovídio Pires de Campos, 333 - Cerqueira César. São Paulo, SP, Brazil. 05403-010.
jgreve@usp.br

ABSTRACT

The new coronavirus, which causes the infectious disease named COVID-19 by the World Health Organization (WHO), was notified in 2020 in China. The main clinical manifestations in infected patients are fever, cough and dyspnoea. These patients are prone to developing cardiac changes, diffuse myopathy, decreased pulmonary function, decreased inspiratory muscle strength, and a deterioration in functional capacity. Thus, it is expected that patients affected by COVID-19 will suffer musculoskeletal consequences as a result of the inflammatory process and loss of muscle mass caused by immobility, generating motor incapacities that are not yet quantifiable. It is important to understand the clinical implications caused by COVID-19, in order to have better rehabilitation strategies for these patients. The aim of this study was to conduct a reflective analysis of the impact of COVID-19 on the immune, neuromuscular and musculoskeletal systems, and its rehabilitation process. This is a reflexive analysis, developed in the Laboratory for the Study of Movement of the Institute of Orthopaedics' and Traumatology, at the Universidade de São Paulo School of Medicine, SP, Brazil. In this analysis, we reflect on the following topics related to COVID-19: immunological mechanisms, impact on the neuromuscular and musculoskeletal systems, and the rehabilitation of patients. ***Level of evidence V; Opinion of the specialist.***

Keywords: COVID-19; Neuromuscular manifestations; Musculoskeletal system; Exercise therapy; Immune system.

RESUMO

O novo coronavírus, que causa a doença infecciosa denominada COVID-19 pela Organização Mundial de Saúde, foi notificado em dezembro, na China. As principais manifestações clínicas dos pacientes infectados são febre, tosse e dispneia. Esses pacientes têm propensão a desenvolver alterações cardíacas, miopatia difusa, diminuição da função pulmonar, diminuição da força muscular inspiratória e deterioração da capacidade funcional. Assim sendo, é esperado que os pacientes afetados pela COVID-19 sofram sequelas musculoesqueléticas em decorrência do processo inflamatório e perda de massa muscular causada pela imobilidade, que geram incapacidades motoras ainda não quantificáveis. Existe a necessidade de entender as implicações clínicas causadas pela COVID-19 para elaborar melhores estratégias de reabilitação para esses pacientes. O objetivo deste estudo foi realizar uma análise reflexiva no que tange ao impacto da COVID-19 nos sistemas imunológico, neuromuscular e musculoesquelético e no processo de reabilitação. Trata-se de uma análise reflexiva, desenvolvida no Laboratório do Estudo do Movimento do Instituto de Ortopedia e Traumatologia da Faculdade de Medicina da Universidade de São Paulo, SP, Brasil. Nesta análise, fizemos uma reflexão sobre os seguintes tópicos relacionados com a COVID-19: mecanismos imunológicos, impacto no sistemas neuromuscular e musculoesquelético e reabilitação dos pacientes. ***Nível de evidência V; Opinião do especialista.***

Descritores: *COVID-19; Manifestações neuromusculares; Sistema musculoesquelético; Terapia por exercício; Sistema imunológico.*

RESUMEN

El nuevo coronavirus, que causa la enfermedad infecciosa llamada COVID-19 por la Organización Mundial de la Salud, fue notificado en diciembre en China. Las principales manifestaciones clínicas de los pacientes infectados son fiebre, tos y disnea. Esos pacientes son propensos a desarrollar cambios cardíacos, miopatía difusa, disminución de la función pulmonar, disminución de la fuerza muscular inspiratoria y deterioro de la capacidad funcional. Por lo tanto, se espera que los pacientes afectados por COVID-19 sufran secuelas musculoesqueléticas debido al proceso inflamatorio y pérdida de masa muscular causada por la inmovilidad, que generan discapacidades motoras aún no son cuantificables. Es necesario comprender las implicaciones clínicas causadas por COVID-19 para elaborar mejores estrategias de rehabilitación para estos pacientes. El objetivo de este estudio fue realizar un análisis reflexivo sobre el impacto de COVID-19, en los sistemas inmunitario, neuromuscular y musculoesquelético

y en el proceso de rehabilitación. Es un análisis reflexivo, desarrollado en el Laboratorio del Estudio de Movimiento del Instituto de Ortopedia y Traumatología, Facultad de Medicina, Universidad de São Paulo, SP. En este análisis, reflexionamos sobre los siguientes temas relacionados con COVID-19: mecanismos inmunológicos, impacto en los sistemas neuromuscular y musculoesquelético y la rehabilitación de los pacientes. ***Nivel de evidencia V; Opinión de expertos.***

Descriptores: *COVID-19; Manifestaciones neuromusculares; Sistema musculoesquelético; Terapia por ejercicio; Sistema inmunitario.*

DOI: http://dx.doi.org/10.1590/1517-869220202604ESP002 Fast tracking

INTRODUCTION

The coronavirus (COVID-19) appeared in China in December 2019, with a high power of dissemination and mortality, especially in the elderly with associated chronic diseases [1-3] evolving with the need for hospitalization due to severe acute respiratory syndrome (SARS)[2-4]. To date, there are no effective pharmaceutical interventions for the treatment of COVID-19, with social detachment being the most effective strategy to decrease community transmission of the virus and the burden on health systems[2-5].

The main clinical manifestations of patients infected with COVID-19 are: fever (88.7%), cough (57.6%) and dyspnea (45.6%). Laboratory tests show decreased levels of albumin (75.8%), increased C-reactive protein (58.3%) and increased lactate dehydrogenase (57%). In imaging exams, bilateral pneumonia (72.9%) is frequently seen and 20.3% of patients require care in an intensive care unit, due to SARS (32.8%), acute myocarditis (13%) and pneumonia (7.9%)[6].

Polyneuropathy in the critical patient (PPC) can occur after infection by COVID-19, being a mixed sensorimotor neuropathy that leads to axonal degeneration[7]. In critical patients admitted to the Intensive Care Unit (ICU), 46% had PPC [8] and 48% to 96% diffuse non-necrotizing myopathy (MPC) with fatty degeneration, hypotrophy and fibrosis[7]. For both PPC and MPC, the cranial nerves and facial muscles are preserved. The recovery process of MPC is faster than that of PPC, however both conditions cause: weakness, loss of function, loss of quality of life and decrease in resistance and can persist for up to two years [9,10]. Thus, PPC and MPC are associated with decreased lung function (restrictive pattern), decreased inspiratory muscle strength with worsening functional capacity, requiring a year or more for recovery[9,10].

Infected patients are also prone to develop cardiac changes after COVID-19, but the mechanism of the injury is still uncertain. They may have arrhythmia, heart failure, decline in ejection fraction, elevated troponin I and severe myocarditis with reduced systolic function [9-11].

Studies have shown that SARS can cause polyneuropathy, viral encephalitis and ischemic stroke. In Middle East Respiratory Syndrome, one fifth of patients had neurological symptoms (altered level of consciousness, paralysis, ischemic stroke, Guillain-Barré syndrome, infectious neuropathy and seizures)[9,12,13].

Thus, it is already expected that patients infected with COVID-19 will suffer musculoskeletal consequences due to the inflammatory process aggravated by the loss of muscle mass from immobilism, generating motor disabilities that are not yet quantifiable. There is a great need to understand the clinical implications caused by COVID-19, in order to have better rehabilitation strategies for these patients. The aim of this study was to conduct a reflective analysis regarding the impact of COVID-19, on the immune, neuromuscular and musculoskeletal systems and their rehabilitation process.

MATERIALS AND METHODS

It is a reflexive analysis, developed in the Laboratory of the Study of Movement of the Institute of Orthopedics and Traumatology, Faculty of Medicine, University of São Paulo, SP, Brazil.

Immunological mechanisms

The direct action of inflammatory cytokines on muscle tissue is one of the mechanisms for reducing musculoskeletal function and trophism. In the SARS-COV-2 inflammatory storm, there is increased expression of the NLRP3 inflammasome, which is a fundamental component of the innate immune system[14]. Viral proteins, such as viropyrines E, 3A and 8A, play an important role in virus replication and activation of NLRP3 [15,16]. NLRP3 acts on the activation of caspase-1 and secretion of the inflammatory cytokines Interleukins IL-1BETA and IL-18 in response to microbial infection or cell damage. The increase in interleukins is linked to several inflammatory disorders and chronic diseases[17]. The increase in IL-1BETA is caused by mitogen-activated proteinokinases (MAP - kinase) and NFk-Beta leading to the production of Interleukin-6 (IL-6). TNF-ALFA AND IFN-GAMA have a synergistic effect by increasing the gene expression of IL-6[18,19]. IL-6, has a strong sarcopenic action, and by increasing atrogin-1 by activating STA3 that causes FoxO3 translocation to the cell nucleus[20-22].

Another mechanism of sarcopenia is local denervation, little considered, caused by the immobilization resulting from the disease. Sedentary lifestyle causes denervation and neural damage at the neuromuscular junction, seen by the measurement of the neuronal cell adhesion molecule (NCAM), a glycoprotein expressed in embryonic life and absent in adults. NCAM-Positive is an indication of denervation and is seen in paralysis, neurodegenerative diseases, immobilism and inactivity[23,24].

The decrease in the expression of the HOMER protein, which makes up the neuromuscular junction (NMR) and the increase in the C-terminal fragment of agrine, confirm the findings of neural damage in the NMR and the sarcopenia caused by immobility[25,26]

Impact of COVID-19 on the neuromuscular system

COVID-19 causes neurological manifestations in 88% of critically ill patients, with dysgeusia being one of the most frequent, and also seen in a patient with a milder condition. Acute cerebrovascular disease (5.7%), changes in consciousness (14.8%) and musculoskeletal involvement (19.3%) are also reported in the most severe patients. These frequencies are, respectively, 7.1, 6.7 and 4 times higher than in moderate cases [27,28]

Although mechanisms are not yet fully known, there is growing evidence that coronaviruses invade peripheral nerve terminals and gain access to the CNS through synaptic pathways[29]. Also, the cribriform plaque or systemic circulation are considered as brain entry pathways. The transsynaptic pathway, however, is already well documented for other coronaviruses (HEV 679-10 and chicken infectious bronchitis virus)[30-34].

The presence of the virus causes an intense systemic inflammation, weakens the blood-brain barrier, making it permeable to viral invasion. It also allows more cytokines from different locations to access the CNS, triggering neuroinflammation[31,35].

Neural invasion needs to be valued due to clinical impacts, especially in the treatment of respiratory failure, due to the need for neuromuscular activation of the diaphragm and accessory muscles. The nuclei

of the solitary tract receive information from the mechanoreceptors and chemoreceptors of the lungs and airways and efferent fibers from the ambiguous nuclei and the solitary tract provide innervation to the smooth muscles of the airways, glands and vasculature. Hence, the suggestion that the death of infected animals or patients may also occur due to cardiorespiratory dysfunction originating in the brain stem[30,32,36].

In SARS-COV-2 infected neural tissue, cells die from apoptosis induced by the virus itself, since inflammatory expression may still be minimal in the tissue[37]. There is great similarity between the apoptotic mechanism and the pathophysiology of demyelinating diseases, which are also seen in SARS-COV-2 infection, such as Guillain-Barré Syndrome and acute myelitis[38,39].

Acute necrotizing hemorrhagic encephalopathy, also present in patients with COVID-19, is associated with inflammation, where hyperketonemia promotes proteolytic destruction of the blood-brain barrier, by the action of trypsin and activation of the metalatoprotease-9 matrix, which increases the permeability vascular, causing edema, petechial hemorrhage and necrosis[40-42].

These polyneuropathies triggered by apoptotic and inflammatory mechanisms, even evidenced in the corticospinal tract, may explain, even partially, the decrease in musculoskeletal trophism[12,43]. Coagulation disorders, characterized by elevation of D-dimer showing hypoperfusion and even small ischemic strokes also need to be considered[41].

Impact of COVID-19 on the system on the musculoskeletal system

Long hospitalizations, isolations and even social distance, affect muscle homeostasis, with the secondary impact of physical inactivity and disuse. The cause of muscle mass loss, most likely, is multifactorial, involving inflammation, immobilization, insufficient nutrition and administration of corticosteroids[44].

In the critical phase of SARS-COV-2 with a long stay in intensive care units, there is a loss of homeostasis between protein synthesis and degradation with gradual reduction in muscle protein renewal. The increase in muscle protein degradation is due to the action of intracellular signaling pathways. The ubiquitin-proteasome system, the main pathway related to the proteolysis mechanism, has two specific enzymes related to the skeletal muscle atrophy process, activated in response to inactivity and the inflammatory process: atrogin-1 (Muscle Atrophy F-box) and MuRF-1 (Muscle Ring Finger -1)[45].

According to Poulsen et al. (2012)[44], septic patients admitted to the ICU have a loss of 20% of thigh muscle mass in the first week of hospitalization. Inflammation associated with immobility is more pronounced at this stage, where metabolic changes explain the higher rate of initial losses.

During hospitalization, muscles, especially those of the lower extremities, are not exposed to mechanical discharges with reduced neuromuscular activity, which stimulates an adaptive response, slow protein synthesis, greater protein degradation, apoptosis of muscle cells (main mechanisms of hypotrophy) and decreased muscle strength. In healthy individuals exposed to immobilization (bed rest), there is a decrease in mass (14%) and muscle strength (16%). Thus, it is possible to deduce that an inflammatory process caused by sepsis associated with immobilism, can promote muscle loss, up to 10 times greater than in healthy people[44].

The skeletal muscle system adapts to prolonged physical inactivity, decreasing the size of the muscle fiber (atrophy), in addition to loss of muscle function and quality. Mechanosensory proteins that allow muscle fibers to detect mechanical forces, are also involved in the regulation of skeletal muscle mass. Its activation, during muscle contraction, regulates protein renewal through interaction with the mechanistic target protein of rapamycin (mTORC1) and with the main proteolytic pathways: the proteasome and lysosomal / autophagic ubiquitin systems[46].

Functional impairments, commonly reported in the literature in critically ill patients, are directly related to the length of stay in the ICU and prolonged mechanical ventilation. Seven days of bed rest can already reduce muscle strength by 30%, with an additional loss of 20% of the remaining strength each week. Deficiencies in physical function and exercise capacity can last for years after discharge from the ICU[47]. Disuse and loss of innervation in diseases or injuries directly affect the musculoskeletal system promoting a decline in muscle mass and strength joint strength and atrophy diffuse and symmetrical striated appendicular and axial skeletal musculature[47].

Respiratory and neuromuscular rehabilitation interventions, recommend the shortest possible time for intubation and improvement of muscle condition are directly associated with the prognosis of patients in the ICU[48]. Evidence of this type of intervention at COVID-19 is still scarce. Patients admitted to the ICU during previous epidemics suffered musculoskeletal injuries and complications that required rehabilitation, with an individualized and dynamic intervention, adapting to the rapid changes that characterize the disease's progression, especially in the first seven days of evolution[49]. Although COVID-19 predominantly affects the respiratory system, evidence indicates a severe and lethal multisystemic disease. Long-term sequelae are not yet known, but evidence of previous coronavirus outbreaks demonstrates functional motor and respiratory impairment, emotional distress and loss of quality of life. Musculoskeletal complications with worsening physical aptitudes are referred: as heterotopic ossification, loss of muscle mass, prolonged pain, weakness and dyspnea. It is estimated that 45% of patients discharged from hospital will require health care and social assistance and 4% will require a rehabilitation program[50].

Rehabilitation

The rehabilitation of COVID-19 patients begins at admission to maintain the functioning of vital systems and continues in the post-admission phase to address the sequelae and complications caused by the virus and a long period of hospitalization.

During hospitalization, early mobilizations in the intensive care unit to prevent and reduce polyneuromyopathy in the critical patient, improves quality of life, reduces time and lower mortality during hospitalization[51]. The early start of a structured rehabilitation program contributes to the optimization of cognitive, respiratory, neuromuscular and osteoarticular function, shortening the duration of ICU stay and its clinical and functional sequelae[52].

The prevention of disabilities in critically ill patients helps the patient's medical management. The physical and cognitive intervention protocols improve the patient's understanding of treatment and psychosocial support programs, the behavior change and adherence to the guidelines[53].

Rehabilitation programs should be adapted to the severity of the disease, the patient's age, previous fitness levels and pre-existing comorbidities. Some essential components for the rehabilitation of patients with COVID-19, will need new knowledge and skills about COVID-19.

The rehabilitation program should start with low-intensity physical exercises, with continuous monitoring of oxygenation and fatigue. Patients who experience throat, body and chest sore associated with shortness of breath, fatigue, cough or fever should exercise more than three METS (PSE greater than 2 or equivalent). If the individual has very mild symptoms that may or may not be caused by COVID-1, mild activities of less than three METS (PSE 9-12 or equivalent) are recommended. Also avoid sedentary lifestyle for long periods is necessary. During physical exercise, rest periods can be increased if symptoms worsen. In people who have had mild or moderate symptoms, stretching exercises and low intensity strength training are recommended before targeted aerobic training sessions[50]. In asymptomatic people who have had contact

with positive COVID-19 people, activity should be continued as normal. Pain management should be centered on the patient involving postural reeducation. Outpatient physical rehabilitation programs vary according to the needs of each patient, but they can last from six to 12 weeks and need to be associated with cognitive rehabilitation[54].

FINAL CONSIDERATIONS

Millions of people around the world are being affected by SARS-COV 2. It has been a great and painful learning experience on how to better cope with serious and lethal illness without drugs and vaccines. How to prevent contagion and spread, how to prevent the worsening of symptoms, how to keep patients alive within the intensive care unit, how to prevent respiratory, physical and psychological sequelae, and finally, how to rehabilitate and return normal life to those affected. Understanding the consequences in the post-epidemic and giving the best treatment to all those affected is the great challenge that has to be faced with scientific knowledge and evidence.

Many of the effects are already known and need to be adequately addressed according to the needs of each patient, but without losing sight of the characteristics of SARS-COV 2, which may require different care and treatments. It is observed that the disease itself and the necessary treatment can generate serious disabilities and that an early approach can be essential for the adequate rehabilitation of patients.

AKNOWLEDGE

"This study was financed in part by the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Finance Code 001".

All authors declare no potential conflict of interest related to this article

AUTHORS' CONTRIBUTIONS: Each author made significant individual contributions to this manuscript. JMG and ACA: critical review of the intellectual content and final approval of the version of the manuscript to be published. GCB: substantial contribution to the conception of the work, critical review of the intellectual content and final approval of the version of the manuscript to be published. MQ and ALSS: substantial contribution to the conception and writing of the work.

REFERENCES

1. Ashour HM, Elkhatib WF, Rahman MM, Elshabrawy HA. Insights into the recent 2019 novel coronavirus (Sars-coV-2) in light of past human coronavirus outbreaks. Pathogens. 2020;9(3):186.
2. Brasil [Ministério da Saúde]. Boletim Epidemiológico 01 - Infecção Humana pelo Novo Coronavírus (2019-nCoV) - Janeiro 2020. Bol Epidemiológico. 2020;2:1–17.
3. Brasil [Ministério da Saúde]. Coronavírus - Plataforma Integrada de Vigilância em Saúde - Ministério da Saúde [Internet]. 2020 [cited 2020 May 21]. Available from: http://plataforma.saude.gov.br/coronavirus/
4. Applegate WB, Ouslander JG. COVID-19 Presents High Risk to Older Persons. J Am Geriatr Soc. 2020;68(4):681.
5. Lewnard JA, Lo NC. Scientific and ethical basis for social-distancing interventions against COVID-19. Lancet Infect Dis. 2020;20(6):631–3.
6. Gutiérrez-ocampo E, Villamizar-peña R, Holguin-rivera Y, Franco-paredes C, Henao-martinez AF, Panizmondolfi A, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information. 2020;34(January).
7. McNeary L, Maltser S, Verduzco-Gutierrez M. Navigating Coronavirus Disease 2019 (Covid-19) in Physiatry: A CAN report for Inpatient Rehabilitation Facilities. PM R. 2020;12(5):512–5.
8. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016;42(5):725–38.
9. Sheehy LM. Considerations for Postacute Rehabilitation for Survivors of COVID-19. JMIR public Heal Surveill. 2020 May 8;6(2):e19462–e19462.
10. Shepherd S, Batra A, Lerner DP. Review of Critical Illness Myopathy and Neuropathy. The Neurohospitalist. 2017;7(1):41–8.
11. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020;10:1–10.
12. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological complications during treatment of middle east respiratory syndrome. J Clin Neurol. 2017;13(3):227–33.
13. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan. 2005;14(3):113–9.
14. Lu M, Yin N, Liu W, Cui X, Chen S, Wang E. Curcumin Ameliorates Diabetic Nephropathy by Suppressing NLRP3 Inflammasome Signaling. Biomed Res Int. 2017;2017:1–10.
15. Shi CS, Nabar NR, Huang NN, Kehrl JH. SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov. 2019;5(1).
16. Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG, et al. The Greek study in the effects of colchicine in COvid-19 complications prevention (GRECCO-19 study): Rationale and study design. Hell J Cardiol. 2020;S1109-9666(20):30061–0.
17. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 inflammasome: An overview of mechanisms of activation and regulation. Int J Mol Sci. 2019;20(13):1–24.
18. De Rossi M. Cytokines and chemokines are both expressed by human myoblasts: possible relevance for the immune pathogenesis of muscle inflammation. Int Immunol. 2000;12(9):1329–35.
19. Luo G, Hershko DD, Robb BW, Wray CJ, Hasselgren PO. IL-1β stimulates IL-6 production in cultured skeletal muscle cells through activation of MAP kinase signaling pathway and NF-κB. Am J Physiol - Regul Integr Comp Physiol. 2003;284(5 53-5):1249–54.
20. Haddad F, Zaldivar F, Cooper DM, Adams GR. IL-6-induced skeletal muscle atrophy. J Appl Physiol. 2005;98(3):911–7.
21. Radigan KA, Nicholson TT, Welch LC, Chi M, Amarelle L, Angulo M, et al. Influenza A Virus Infection Induces Muscle Wasting via IL-6 Regulation of the E3 Ubiquitin Ligase Atrogin-1. J Immunol. 2019;202(2):484–93.
22. Min A, Baltgalvis KA, Berger FG, Peña MMO, Davis JM, White JP, et al. NIH Public Access. 2010;457(5):989–1001.
23. Arentson-Lantz EJ, English KL, Paddon-Jones D, Fry CS. Fourteen days of bed rest induces a decline in satellite cell content and robust atrophy of skeletal muscle fibers in middle-aged adults. J Appl Physiol. 2016;120(8):965–75.
24. Demangel R, Treffel L, Py G, Brioche T, Pagano AF, Bareille MP, et al. Early structural and functional signature of 3-day human skeletal muscle disuse using the dry immersion model. J Physiol. 2017;595(13):4301–15.
25. Drey M, Sieber CC, Bauer JM, Uter W, Dahinden P, Fariello RG, et al. C-terminal Agrin Fragment as a potential marker for sarcopenia caused by degeneration of the neuromuscular junction. Exp Gerontol. 2013;48(1):76–80.
26. Narici M, De Vito G, Franchi M, Paoli A, Moro T, Marcolin G, et al. Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: Physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. Eur J Sport Sci. 2020;0(0):1–22.
27. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Oto-Rhino-Laryngology. 2020;2:1–11.
28. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;1–8.
29. Dubé M, Coupanec L, Wong AHM, Rini JM, Desforges M, Talbot J. Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43. J Virol. 2018;92(17):1–21.
30. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS Neurosci Ther. 2020;26(5):499–501.
31. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.
32. Li YC, Bai WZ, Hirano N, Hayashida T, Hashikawa T. Coronavirus infection of rat dorsal root ganglia: Ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. Virus Res. 2012;163(2):628–35.
33. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92(6):552–5.
34. Zhou L, Zhang M, Gao J, Wang J. Sars-Cov-2: Underestimated damage to nervous system. Travel Med Infect Dis. 2020;101642.
35. De Felice FG, Tovar-Moll F, Moll J, Munoz DP, Ferreira ST. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Central Nervous System. Trends Neurosci. 2020;1–3.
36. Matsuda K, Park CH, Sunden Y, Kimura T, Ochiai K, Kida H, et al. The vagus nerve is one route of transneural invasion for intranasally inoculated influenza A virus in mice. Vet Pathol. 2004;41(2):101–7.
37. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe Acute Respiratory Syndrome Coronavirus Infection Causes Neuronal Death in the Absence of Encephalitis in Mice Transgenic for Human ACE2. 2008;82(15):7264–75.
38. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection : A case report. J Clin Neurosci. 2020;76:233–5.
39. Toscano et al. Guillain – Barré Syndrome Associated with SARS-CoV-2. New Engl J Med NEJMc2009191. 2020;17–9.
40. Ichiyama T, Endo S, Kaneko M, Isumi H, Matsubara T, Furukawa S. Serum cytokine concentrations of influenza-associated acute necrotizing encephalopathy. 2003;(September 2002):734–6.
41. K. Chong Ng Kee Kwong, P.R. Mehta, G. Shukla ARM. COVID-19, SARS and MERS: A neurological perspective. J Clin Neurosci. 2020;77:13–6.
42. Kansagra SM, Do WBG. Pediatric Neurology Cytokine Storm of Acute Necrotizing Encephalopathy. Pediatr Neurol. 2011;45(6):400–2.
43. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17(5):259–60.
44. Poulsen JB. Impaired physical function, loss of muscle mass and assessment of biomechanical properties in critical ill patients. Dan Med J. 2012;59(11):1–21.
45. Mesquita TM de JC, Gardenghi G. Imobilismo e fraqueza muscular adquirida na unidade de terapia intensiva. Rev Bras Saúde Func. 2016;1(3):1–12.
46. Woods J, Hutchinson NT, Powers SK, Roberts WO, Gomez-Cabrera MC, Radak Z, et al. The COVID-19 Pandemic and Physical Activity. Sport Med Heal Sci. 2020;
47. Mendez-Tellez PA, Nusr R, Needham DM, Feldman D. Early Physical Rehabilitation in the ICU: A Review for the Neurohospitalist. The Neurohospitalist. 2012;2(3):96–105.
48. Stiller K. Physiotherapy in intensive care: An updated systematic review. Chest. 2013;144(3):825–47.
49. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370(17):1626–35.
50. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med. 2020;1–11.
51. Dantas CM, Silva PF dos S, Siqueira FHT de, Pinto RMF, Matias S, Maciel C, et al. Influência da mobilização precoce na força muscular periférica e respiratória em pacientes críticos. Rev Bras Ter Intensiva. 2012;24(2):173–8.
52. Zhao HM, Xie YX, Wang C. Recommendations for respiratory rehabilitation in adults with COVID-19. Chin Med J (Engl). 2020;
53. Johnston CL, Maxwell LJ, Alison JA. Pulmonary rehabilitation in Australia: A national survey. Physiotherapy. 2011;97:284–9.
54. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: An overview. J Transl Intern Med. 2017;5(5):90–2.