The impact of SARS-CoV-2 on skeletal muscles

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In 2019-2020, the SARS-CoV-2 pandemic has shocked the world and most health care systems, and a “second wave” of the viral spread is ongoing in Europe and in Italy too. While, at the initial outbreak, the treatment of patients had focused on the respiratory symptoms, many diverse clinical manifestations of the disease have to date been reported. However, the complete course of the disease has not yet been fully clarified. In particular, several reports from the real-world clinical practice have highlighted the noxious effects of SARS-CoV-2 on skeletal muscles. In this brief review, we summarized the main current findings about muscular and neuromuscular damages that may be triggered by the virus or by the drugs used to treat COVID-19. Moreover, we underlined the need of attentive care and vigilance for patients with neuro-muscular disorders, who may be particularly susceptible to infection and at increased risk for severe COVID-19.

Key words: SARS-CoV-2, COVID-19, skeletal muscles

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel beta-coronavirus that causes a diverse range of symptoms in patients, now defined as coronavirus disease (COVID-19). Declared as a pandemic on 11 March 2020 by the World Health Organization (WHO), it has currently affected (as of October 2020) more 37 million people worldwide and caused more than 1 million of deaths¹. So far, the fatality rate due to COVID-19 varies from 1% to more than 7% and the main cause of death remains a respiratory failure. However, the complete course of the disease has not yet been fully clarified and little is presently known about the long-term effects of the infection on physiology and health conditions.

At the initial outbreak of the pandemic, the treatment of patients focused on the respiratory symptoms, and thus on the management of fever, cough, shortness of breath, and respiratory failure. With the months and virus worldwide spread following the initial outbreak, it has become increasingly evident that SARS-CoV-2 infection may cause a large variety of other symptoms, including significant central and peripheral neurological manifestations of the disease².

This brief review aims at highlighting the main findings about the effects of SARS-CoV-2 infection and the potential damages directly and indirectly caused by COVID-19 on skeletal muscles. The so far suggested patho-physiology mechanisms are also mentioned. We analyzed the relevant reports on the topics published on PubMed until 12th October 2020. Additionally, we performed a focused literature search in the same data-

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Biology and pathophysiology of neurological and muscular damages caused by SARS-CoV-2

The binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) has a pivotal role in the pathophysiology of clinical manifestations in patients with COVID-19. ACE2 is widely expressed on multiple organs including nose, lungs, kidneys, liver, blood vessels, immune system, skeletal muscles and brain. Skeletal muscles in particular, and other cells in the muscles like satellite cells, leukocytes, fibroblasts, and endothelial cells, express ACE-2. Therefore, it is postulated that skeletal muscles are also susceptible to direct muscle invasion by SARS-CoV-2. Moreover, after binding ACE2 and invading cells, SARS-CoV-2 may cause a "cytokine storm", with marked elevation in levels of interleukin-1, interleukin-6, and tumor necrosis factor. High levels of these cytokines increase vascular permeability, edema, and widespread inflammation with consequent damage in multiple organs, including nerves and muscles. The cytokine storm also triggers hypercoagulation cascades to cause small and large blood clots. Combined hyperactivation of inflammatory markers, vascular injury, and coagulation factors contributes to Acute Respiratory Distress Syndrome (ARDS), kidney failure, liver injury, heart failure, myocardial infarction, as well as multiple neurological conditions. A direct entry of SARS-CoV-2 into the brain has been described for other coronaviruses and may play a role in SARS-CoV-2’s possible contribution to demyelination or neurodegeneration. Furthermore, the cytokines activated by SARS-CoV-2 can also trigger vasculitis in and around nerves and muscles, with or without a molecular mimicry, intended as cross-reactivity of immunoglobulins (formed in response to the viral antigens) with specific proteins on the myelin, axon, or neuromuscular junction. A direct invasion by the virus to the peripheral nerves may also potentially occur, however a prevalent immune-mediated etiology for peripheral and cranial neuropathies as well as damages to muscles in patients with COVID-19 represents a realistic hypothesis.

Neurological, muscular, and rheumatic skeletal muscle clinical manifestations of COVID-19 (Tab. I)

As SARS-CoV-2 presents neurotropic properties, neurological disease manifestations may occur in both symptomatic and asymptomatic patients. In particular, various neurological manifestations have been described in COVID-19 patients, involving the central nervous system, peripheral nervous system, and skeletal muscles. Importantly, neurological manifestations could appear alone and might present as non-specific symptoms. According to several published studies, patients with severe COVID-19 are more likely to develop neurological dysfunctions, among which acute cerebrovascular disease, consciousness disturbance, encephalopathy, prominent agitation and confusion, ischemic strokes of acute onset, or corticospinal tract signs. Some patients manifest only neurological symptoms, including headache, tiredness, malaise and signs of cerebral hemorrhage, or cerebral infarction. Cases of encephalitis, necrotizing hemorrhagic encephalopathy, strokes, epileptic seizures, or rhabdomyolysis associated with SARS-CoV-2 infection have also been described. Facial weakness, difficulty breathing, being unable to stand or walk, or having difficulty weaning off respiratory ventilators may be in part due to Guillain-Barre syndrome (GBS) caused by COVID-19, as described in some reports. Roman et al., on behalf of the World Federation of Neurology, have recently stressed the urgent need for international neuro-epidemiological collaboration in order to create local registries of cases with neurological manifestations and better define the short-term and long-term neurology of COVID-19.

SARS-CoV-2, similar to SARS-CoV-1, can cause serious injury to cranial nerves, peripheral nerves, and muscles. Muscle weakness, fatigue or myalgia, and muscle atrophy are among the most commonly reported symptoms by patients with COVID-19. For instance, the prevalence of myalgia among currently published reports may range from 21% to more than 50% of affected patients. Moreover, myalgia tends to persist after cessation of viral shedding for a median time of 23 days. In a retrospective study by Zhang et al., muscle ache was one of the independent predictors for worsening of symptoms and disease status in patients with COVID-19. In a Chinese retrospective case series by Mao et al., one of the first reports, conducted on 214 COVID-19 patients hospitalized in Wuhan, 8.9% presented peripheral nerve disease, and 7% had muscular injuries. Moreover, among patients with severe COVID-19, 19.3% had evidence of muscle injury. Similar findings have been reported for COVID-19 patients in other ICU settings. Furthermore, hematologic biomarkers of inflammation, cardiac and muscle injury were found to be significantly elevated in patients with both severe and fatal COVID-19. Consistently, some reports have described patients with COVID-19-related myositis and rhabdomyolysis. All these patients presented elevated serum CK levels, as well as high serum levels of CRP, LDH and ferritin. In addition to myositis and rhabdomyolysis, critical-ill-
ness myopathies, cachexia and sarcopenia have also been described in patients with COVID-19. While there are no current reports of de-novo cases of myasthenia gravis caused by COVID-19, episodes of SARS-CoV-2-related exacerbation of pre-existing myasthenia gravis have been recently reported.

On the other hand, the immune dysregulation caused by COVID-19 may trigger or worsen auto-immunity and rheumatic disorders in genetically susceptible subjects. Several atypical clinical and laboratory manifestations of the disease mimicking rheumatic skeletal muscle diseases (RMDs) have been reported, including musculoskeletal and cardiovascular manifestations, as well as multisystem auto-inflammatory/auto-immunitory syndromes. In addition, laboratory reports of positive antinuclear antibodies (ANA), antiphospholipid antibodies, lupus anti-coagulant assay and increased level of D-dimer have been reported with COVID-19, suggesting the risk for persisting intermediate to long-term immune dysregulation.

Furthermore, the potential adverse effects of antiviral or immune-modulating therapies used to treat COVID-19 should be attentively monitored and analyzed, as several findings of musculoskeletal adverse reactions following the use of these drugs have been reported.

### Impact of drugs with known iatrogenic effects on skeletal muscle in COVID-19 patients

As known, several drugs used for diverse therapeutic interventions may cause adverse effects and toxicities in skeletal muscle tissues. A drug-induced, also defined as “toxic”, myopathy is the acute or subacute manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine kinase (CK) elevation, or myoglobinuria in patients with no pre-existing muscle diseases when exposed to certain classes of drugs. Many of these symptoms have been previously mentioned in this article as potential COVID-19 clinical signs. Drugs can cause muscle tissue toxicity through different mechanisms, for instance by directly affecting muscle organelles such as mitochondria, lysosomes, or myofibrillar proteins; or by triggering immunologic or inflammatory reactions; or by disrupting of electrolyte or nutritional balance, thus compromising the muscle physiologic functions. The medications most commonly associated with toxic myopathy include statins, amiodarone, chloroquine, hydroxychloroquine, colchicine, certain antivirals, and corticosteroids. Some of these drugs have been used and are being currently used to treat patients with COVID-19, more often at an advanced stage of the disease. For instance, as also shown in Table II, a long-term treatment with chloroquine and hydroxychloroquine may cause myopathy and neuro-myopathy, while arthralgia, back pain, osteonecrosis, and vasculitis may occur during lopinavir-ritonavir therapy; musculoskeletal pain and myalgia may follow interferon therapy, which rarely can also lead to drug-induced RMDs, such as rheumatoid arthritis, lupus, Sjogren syndrome and myositis, sarcoidosis, and vasculitis. On the other hand, the current safety profile of remdesivir, one of the anti-virals mainly used to treat COVID-19 worldwide, is still incomplete and, to date, has shown no adverse reactions on muscles. We suggest it is important for clinicians to be aware of iatrogenic effects of certain classes of drugs on skeletal muscle, especially for the following reasons: 1) some of the COVID-19 symptoms on muscles may shadow the toxicities caused by COVID-19 treating drugs and thus let them unrecognized, causing irreversible damages; 2) the noxious effects on skeletal muscles of COVID-19 and drugs used to treat COVID-19 might add up and worsen the symptoms and injuries caused; 3) the effects on muscles of all drugs currently used to treat COVID-19 on large populations of patients, such as remdesivir and corticosteroids, should be attentively monitored and signaled to pharmacovigilance authorities; 4) the use of COVID-19 drugs with potential adverse effects on muscles should be attentively considered and weight in patients who already receive other agents known to be toxic on muscle tissues, such as statins; 5) the use of COVID-19 drugs with potential adverse effects on muscles should be attentively considered and weighted in patients with pre-existing neuromuscular disorders.

| Classification | Clinical manifestations and symptoms of COVID-19 |
|----------------|--------------------------------------------------|
| Neurological   | Acute cerebrovascular disease, consciousness disturbance, encephalopathy, prominent agitation and confusion, acute ischemic strokes, headache, tiredness, malaise, cerebral hemorrhage, cerebral infarction, encephalitis, necrotizing hemorrhagic encephalopathy, strokes, epileptic seizures |
| Neuromuscular  | Muscle weakness, fatigue or myalgia, and muscle atrophy, peripheral nerve disease, muscle injury, myositis and rhabdomyolysis, exacerbations of myasthenia gravis |
| Rheumatic      | Cytokine storm/Secondary Hemophagocytic lymphohistiocytosis (sHLH), Guillain-Barré syndrome (GBS), Kawasaki-like disease |

Table I. Main reported neurological, muscular and rheumatic clinical signs and symptoms associated with COVID-19.
COVID-19 in patients with neuromuscular disorders

Given the neurotropic properties and neuro-invasive potential of SARS-CoV-2, a special attention should be addressed to patients with pre-existing neuromuscular disorders, including muscle disorders (e.g., muscular dystrophies, congenital myopathies, metabolic myopathies, inflammatory myopathies, and muscle channelopathies), diseases of the neuromuscular junction (e.g., either acquired or congenital myasthenic syndromes), peripheral nerve disorders (e.g., dysimmune neuropathies, familial amyloid neuropathies, and Charcot-Marie-Tooth disease), and spinal muscular atrophies, in order to prevent and early recognize neuromuscular complications that may be – directly or indirectly – related to the viral infections. These diseases constitute a group of very heterogeneous conditions, most often of genetic or autoimmune origin, and can affect both children and adults to a degree that varies widely from one individual to another. A few reports on the topic have been recently published and stressed the need for clinical research to develop evidence-based guidelines to minimize morbidity and mortality due to COVID-19 in patients with neuromuscular disorders. As explained in a complete review by Guidon A and Amato A, the risks for these patients depend on several factors, including the specific neuromuscular disease, other co-morbidities, age, and type of immuno-therapy they receive. In highly susceptible patients, it is hypothesized that novel disorders such as Guillain-Barré Syndrome, myopathies, myositis and polyneuropathies may occur. Case reports have recently been published proving this risk, which is related to immune dysregulation and molecular mimicry between specific viral antigens and proteins expressed on peripheral nerves, ultimately causing auto-immune damages on myelin or axon of peripheral nerves. A probably more significant risk resided in the exacerbation or disease progression of pre-existing rare neuromuscular disorders, or the unmasking of previously unrecognized ones, both inherited and immune-mediated. As mentioned, according to a recent retrospective study, COVID-19 has caused the exacerbation of myasthenia gravis. Experts are therefore expecting increased rates of disease worsening and incidence of novel diagnoses during the pandemic, and in March 2020 the Association of British Neurologists had already published a “guidance on COVID-19 for people with neurological conditions, their doctors and carers”. A guidance has also been released in June by the French Rare Health Care for Neuromuscular Diseases Network. These guidelines suggest that patients with motor neuron diseases (e.g., amyotrophic lateral sclerosis, spinal muscular atrophy) and hereditary neuropathies, and patients with various muscular dystrophies, including myotonic dystrophy, and metabolic diseases (e.g., Pompe disease), who present ventilatory muscle involvement or cardiomyopathy may be particularly susceptible to infection and at increased risk for severe COVID-19. Moreover, patients with metabolic myopathies (e.g., lipid storage diseases and mitochondrial disorders) are at increased risk of rhabdomyolysis. It is also postulated that patients who develop COVID-19 may not return to their prior baseline. Furthermore, use of immunosuppressive therapies may put patients with neuromuscular disorders at increased risk of contracting COVID-19 and developing more severe symptoms. In general, experts recommend patients to continue their treatments with steroid/immunosuppressants in the absence of any manifestations suggestive of COVID-19, and avoid sudden interruptions that may trigger a disease flare. In case of COVID-19 symptoms, patients may temporarily hold the therapy based on their neurologist advice. Interestingly,
a recent Italian survey conducted in specialized neuromuscular centers has pointed out a significant disruption of clinical and support services for patients with neuromuscular diseases in the acute phase of the pandemic, particularly in terms of rehabilitative services and on-site outpatient visits. The expected (or actually ongoing) “second wave” of the virus spread should not find our systems unprepared but instead accelerate the adoption of novel modalities, including telemedicine services, for ensuring quality care and thorough monitoring to patients with neuromuscular disorders.

Conclusions

The SARS-CoV-2 pandemic has shocked the world and most health care systems, even in wealthy nations with advanced and renowned systems. Following the initial outbreak and the extensive efforts in all fields of clinical research, more and more evidence is being brought out and shared in order to tackle and, with effective treatments and vaccines, eradicate the virus and the disease. Many reports have highlighted the clinical manifestations caused by the effects of SARS-CoV-2 on muscles. Several research teams are currently investigating the muscular and neuromuscular damages that may be triggered by the virus or by the drugs used to treat COVID-19. In this review, we summarized the state-of-the-art on the topic and suggest a more thorough attention on symptoms and laboratory markers of muscle damages, especially considering that some of the therapies used to treat COVID-19 may be toxic on muscles. Finally, patients with RMDs and patients with auto-immune or genetic neuromuscular disorders should be attentively monitored for exacerbation of symptoms or disease flares. Based on a recent search on clinicaltrials.gov (as of October 12th 2020), we only found 5 clinical studies about COVID-19 and muscle, 4 of which are observational studies or disease registries in special populations of patients (patients with neuromuscular disorders and patients with inflammatory rheumatic diseases). While real-world evidence is essential for the understanding of the disease, especially considering the long-term effects of the viral infection, pharmacovigilance registries and experimental trials are also needed. It is about time for governments to substantially finance independent rigorous clinical research and encourage research networks and public sharing of findings.

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