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 website.

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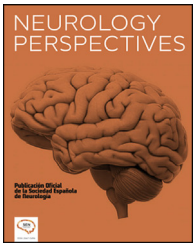

REVIEW

Post-COVID symptoms of potential peripheral nervous and muscular origin

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Abstract Many patients report persistent symptoms attributable to dysfunction of the peripheral nervous and muscular systems after acute COVID-19. These symptoms may constitute part of the so-called post–acute COVID-19 syndrome (PACS), or may result from neuromuscular complications of hospitalisation in intensive care units (ICUs). This article provides an updated review of symptoms of potential neuromuscular origin in patients with PACS, differentiating symptoms according to muscle, peripheral nerve, or autonomic nervous system involvement, and analyses the forms of neuromuscular involvement in patients who were admitted to the ICU due to severe COVID-19.

PALABRAS CLAVE
COVID-19;
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Síntomas post-COVID-19 de posible origen en sistema nervioso periférico y muscular

Resumen Los pacientes que han padecido COVID-19 frecuentemente refieren síntomas persistentes atribuibles a disfunción del sistema nervioso periférico y muscular. Estos síntomas pueden formar parte del denominado síndrome COVID-19 post-agudo (*post-acute COVID-19 syndrome* o PACS) o pueden surgir como consecuencia de las complicaciones neuromusculares del ingreso en unidades de cuidados intensivos (UCI). En este manuscrito se realiza una revisión actualizada de los síntomas de potencial origen neuromuscular en pacientes afectos de PACS, diferenciándolos en función de su posible origen a nivel de músculo, nervio periférico o sistema nervioso autónomo, así como las formas de afectación neuromuscular en pacientes que precisaron ingreso en UCI por COVID-19 grave.

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Introduction

Persistent symptoms after acute SARS-CoV-2 infection encompass a broad spectrum of alterations, and can be long-lasting.[1] While numerous terms (e.g., persistent COVID-19, post–COVID-19 syndrome) have been used to describe these symptoms, there is currently a degree of consensus that they may be grouped together under the term post–acute COVID-19 syndrome (PACS). Different studies define this entity as the persistence of symptoms and/or complications of acute SARS-CoV-2 infection beyond 4–12 weeks after onset of the initial symptoms.[2–5]

Common symptoms reported by patients with PACS include signs suggestive of peripheral nervous and muscular system involvement, such as myalgia, weakness, or exercise intolerance; sensory symptoms (mainly positive symptoms, such as paraesthesia and neuropathic pain); and dysautonomic symptoms.[1–3,6]

In patients with severe COVID-19 and prolonged stays at intensive care units (ICUs), we often observe signs of neuromuscular involvement due to critical illness myopathy and polyneuropathy (CIM and CIP, respectively), as well as focal neuropathies due to nerve entrapment secondary to repositioning or prolonged periods in bed.[7–9]

This article provides an updated review of symptoms of potential neuromuscular origin in patients with PACS, differentiating symptoms according to muscle, peripheral nerve, or autonomic nervous system involvement, and analyses the forms of neuromuscular involvement in patients admitted to the ICU due to severe COVID-19.

Symptoms of possible muscular origin

The most common symptoms of possible muscular origin in patients with PACS are weakness, exercise intolerance, and myalgia. While fatigue or asthaenia is probably the most frequent symptom in these patients, persisting with variable intensity in up to 70% of cases,[6,10] its aetiology is currently considered more likely to be multifactorial than explained by skeletal muscle involvement; therefore, it is not addressed in this section.

Persistent weakness, exercise intolerance, and myalgia are most frequently reported after mild COVID-19. One of the most methodologically appropriate descriptive series published to date included 30 patients with PACS, 29 of whom presented mild initial infection and were treated and followed up on an outpatient basis. In that series, 53.3% of patients presented persistent myalgia at 12 weeks, manifesting during the initial infection in 76.7% of cases. Despite initial recovery, muscle pain reappeared after a period of approximately 3 weeks in 56.7% of patients; however, like other symptoms on the clinical spectrum of PACS, most patients (93%) presented a cyclic pattern with periods of remission and exacerbation.[5] While that study does not specifically comment on weakness or exercise intolerance, another series of 84 patients with PACS found that up to 68% of patients presented signs of weakness at 6 weeks after the initial infection; the latter series differentiates weakness from fatigue.[11] In a third study, reporting 6 months of follow-up data from a sample of 1655 patients hospitalised due to COVID-19, up to 63% of patients reported symptoms of weakness, although this study also included fatigue in the same category.[12]

None of the series discussed above included studies of markers of muscle damage, such as creatine kinase, or electromyography studies. However, another recent study including 20 patients with persistent weakness in the context of PACS did include electrophysiological and laboratory studies at 6 months, and compared the results against paired controls.[13] Only 1 of the 12 patients in whom creatine kinase values were determined showed elevated levels (204 U/L; normal range, 50–150). The same study included a quantitative electromyographic assessment, mainly of the biceps brachii, vastus medialis, and tibialis anterior muscles, and found that 11 patients (55%) presented myopathic changes including reduced duration of motor unit potentials (MUP), with or without decreased amplitude or increased polyphasia; MUP duration presented significant differences as compared to controls in all of the muscles evaluated. However, MUP amplitude was not outside the age- and sex-adjusted 95% confidence interval. It is noteworthy that 50% of patients showing myopathic changes in the electromyography study presented mild-to-moderate initial infections.[13]

Another publication suggesting myopathic changes after mild COVID-19 is a case report describing a young woman who presented persistent proximal weakness and exercise intolerance 3 weeks after mild SARS-CoV-2 infection.[14] The interest of this case report lies in the fact that, before the COVID-19 pandemic, the patient was included as a healthy control in a study using multi-fibre muscle velocity recovery cycles, a technique that evaluates muscle membrane depolarisation and can be used to study a range of different muscle disorders. A repeated study conducted after SARS-CoV-2 infection demonstrated increased excitability of the muscle membrane in the tibialis anterior muscle; biopsy also showed a reduced myosin/actin ratio in the same muscle, a typical finding in patients with CIM. Together, these data suggest that muscle fibres present structural and functional changes in patients with persistent weakness after COVID-19.[14,15]

Since the outset of the pandemic, symptoms of possible skeletal muscle origin have frequently been described, affecting up to 50% of patients in large case series.[16,17] However, the precise mechanisms underlying the potential muscle damage are unknown. While more exhaustive clinical studies are usually not performed, some cases have been described of myopathy of probable inflammatory origin[18] and rhabdomyolysis[19] as form of presentation of SARS-CoV-2 infection. In 2020, the first case was described of COVID-19 presenting with myopathy induced by deposition of

myxovirus resistance protein A (MxA), a protein whose expression is induced by interferon in response to viral infection.[20] This finding is relevant in the light of the results of a recent autopsy study of muscle and nerve samples from 35 patients who died due to COVID-19.[21] The authors report evidence of inflammatory or immune-mediated myopathy in 24 patients (69%), with necrotic fibres, inflammatory infiltrates, and diffuse or multifocal expression of major histocompatibility complex class I (MHC-I) in non-necrotic/non-regenerating fibres. Nine patients (26%), seven of whom showed signs of necrotising myopathy or myositis, presented abnormal MxA immunostaining, mainly in muscle capillaries, suggesting overexpression of type 1 interferon in response to infection.[21] Another autopsy study analysed striated muscle tissue from 42 patients who died due to severe COVID-19, with most samples displaying signs of myositis of varying intensity. Twenty-three patients (55%) presented overexpression of MHC-I antigens, and seven (17%) presented MHC-II overexpression; neither of these findings were observed in the autopsies performed in any of the 11 controls.[22]

Therefore, it is possible that in patients with acute and severe forms of COVID-19, muscle involvement may be explained by an exaggerated immune response (e.g., type 1 interferon overexpression or cytokine storm), or immune-mediated.[21,22] However, further research is needed to clarify the precise pathophysiology of the signs and symptoms suggestive of muscle damage in patients with PACS.

Symptoms of possible peripheral nervous origin

Patients with PACS also frequently present symptoms of possible peripheral nervous origin, mainly positive sensory alterations such as paraesthesia and neuropathic pain. In the previously mentioned series of 30 patients with PACS, diffuse paraesthesias and burning pain were observed in 60% and 43.4% of cases, respectively, and the Neuropathic Pain 4 Questions questionnaire yielded positive results in 50% of cases.[5] In another series of 100 patients with PACS, paraesthesias and other types of sensory alterations were reported by 38% and 15% of patients, respectively, at 4 weeks after the acute infection.[23] That study analysed the distribution of post–COVID-19 symptoms according to severity of the initial infection, finding no significant differences between groups (mild, severe, or critical cases) with regard to the frequency of paraesthesia.[23]

Pain in these patients is frequently described as neuropathic (e.g., burning quality) and associated with typically positive sensory symptoms including paraesthesia or allodynia.[6,23] It has also been described as radicular.[24] While the available studies do not describe pain distribution in detail, localised pain in the feet or legs has been reported, as well as initially generalised and subsequently distal limb pain.[23–25] In clinical practice, neuropathic pain in patients with PACS frequently presents a variable course, with acute exacerbations or attacks.

The neuropathies observed in patients admitted to ICUs due to severe COVID-19 are addressed in detail below; however, cases of isolated or multiple mononeuropathies or brachial plexopathies may also occur in patients with mild-to-moderate COVID-19, and therefore represent a cause of persistent sensory or motor symptoms.[26–31] In our own clinical practice, we have observed several cases of isolated or multiple mononeuropathies, particularly involving the median, ulnar, and lateral femoral cutaneous nerves at the typical entrapment sites, in patients with PACS, including those who presented mild acute COVID-19. Similar cases were described in a recent, unpublished communication.[32] Some of the cases observed by the authors of this review presented partial motor nerve conduction block in nerve conduction studies. The literature includes additional reports of partial motor nerve conduction block in the upper limbs in patients with mild acute COVID-19.[30,33]

As with muscle involvement, few studies report anatomical pathology findings from peripheral nerve tissue samples from patients who died due to COVID-19. The authors of the previously mentioned autopsy study of 35 patients who died due to COVID-19 obtained samples from the femoral nerve, detecting perivascular and/or endoneurial inflammatory infiltrates (neuritis) in nine patients (26%) and capillary MxA expression in seven (20%; only one with neuritis). These data suggest that in at least some patients with severe COVID-19, nerve damage may be caused by an exaggerated immune response similar to that described in muscles.[21] However, the underlying pathophysiological mechanisms remain unclear in most patients with PACS and signs or symptoms of peripheral nerve damage.

Symptoms of possible dysautonomic origin

One relevant issue in the study of patients with PACS is the presence of signs and symptoms secondary to alterations to the autonomic nervous system.[3,34,35] These signs include orthostatic hypotension or intolerance, postural tachycardia, and alterations to sweating, intestinal, or urinary function. These symptoms may occur simultaneously, and are included under the term autonomic dysfunction.

Orthostatic intolerance syndromes, including postural orthostatic tachycardia syndrome, are common autonomic alterations after viral infection.[36–38] Since the first studies of patients with PACS, numerous cases have been reported of orthostatic intolerance syndromes, sometimes associated with alterations in sweating function, intolerance to heat, intestinal or urinary alterations, or small-fibre neuropathy.[34,35,39–43]

A study conducted at the Mayo Clinic included 27 patients with PACS and symptoms of probable dysautonomic origin.[35] All patients underwent comprehensive testing, including studies of sudomotor, cardiovagal, and cardiovascular adrenergic function. Onset of symptoms occurred during the acute stage in 41% of patients and after acute infection in 59% (median, 7 days; range, 0–122). Median progression time was 119 days at the time testing was conducted. Fifty-nine percent of patients were women, and the mean age of the sample was 30 years; this is consistent with the epidemiological profile of patients with PACS attended at neurology departments, in our own experience. The most frequent symptoms included light-headedness, orthostatic headache, syncope, hyperhidrosis, postural tachycardia, and flushing. Such symptoms as hypohidrosis, Sjögren syndrome, intolerance to heat, urinary alterations, early satiety, blurred vision, allodynia, and numbness were rare. The most common clinical syndromes were orthostatic intolerance without demonstrable orthostatic tachycardia or

hypotension in the tests conducted (subjective orthostatic intolerance), in 11 patients (41%), followed by postural tachycardia syndrome (6 patients; 22%) and mild orthostatic intolerance (3 patients; 11%). Other diagnoses included isolated cases of autoimmune autonomic ganglionopathy and exacerbation of pre-existing autonomic or small-fibre neuropathy.[35] Another recent article describes 6 women between 26 and 50 years of age who presented orthostatic intolerance and resting/postural tachycardia and/or hypotension after possible or confirmed COVID-19.[34]

Other symptoms reported by patients with PACS include "brain fog" and floating head sensation. One theory explaining these symptoms proposes the existence of insufficient cerebral vascular self-regulation during prolonged standing, a concept known as orthostatic hypoperfusion syndrome.[39,44] One patient with PACS and this type of symptoms presented a 21% reduction in cerebral blood flow velocity in the middle cerebral artery at 10 min in the tilt test (normal decline, <14%); symptoms improved with administration of intravenous immunoglobulins, which the author considers to be indicative of immune-mediated dysautonomia.[39]

It should be stressed that we currently lack sufficient evidence regarding the use of immunotherapy, including non-specific human intravenous immunoglobulins, in patients with PACS. In our opinion, empirical use of these treatments is not advisable or generalisable on account of the loss of benefit described and the potential adverse effects.

Critical illness myopathy due to COVID-19

The COVID-19 pandemic has led to an unprecedented rise in the incidence of acute respiratory distress syndrome and post–intensive care syndrome. As a result of long ICU stays and associated treatments due to severe COVID-19, we should expect to observe ICU-acquired weakness in these patients.[45]

The available evidence on ICU-acquired weakness after COVID-19 is currently limited to observational studies, most of which are descriptive: case reports and case series on the main associated entities, CIM and CIP. These entities are typically described as generalised flaccid limb muscle weakness and mechanical ventilation weaning failure[9,46–48]; these clinical manifestations do not differ from those observed in patients with non–COVID-associated CIM/CIP.[49]

In a prospective study of patients admitted to ICU due to COVID-19, 11 out of a total of 111 patients (10%) developed CIM/CIP. Compared to patients who did not develop weakness, patients with CIM/CIP were more frequently men with high body mass index, and stayed longer at the ICU; presented more thromboembolic events; received invasive ventilation on more days; presented greater prevalence of treatment with vasoactive drugs, anaesthetics, opioids, and neuromuscular blockers; and more frequently received kidney replacement therapy (continuous veno-venous haemodialysis).[9]

Recovery in these cases is usually progressive and slow, with many patients requiring several weeks or months of intensive motor rehabilitation. A prospective study of 25 patients presenting muscle weakness during hospitalisation at the ICU due to COVID-19 conducted follow-up telephone interviews 1 month after the first assessment, finding that 36% of patients were unable to walk independently and 92% continued to present some degree of muscle weakness.[48]

Critically ill patients with COVID-19 may also present focal neuropathies.[7,49,50] While it is not a specific characteristic of COVID-19, recent case series suggest high prevalence of focal peripheral nerve lesions associated with prone positioning of patients with acute respiratory distress syndrome secondary to severe COVID-19.[7] This possible tendency to develop focal neuropathies may be of multifactorial origin, including direct damage due to traction or compression during prone positioning; such comorbidities as advanced age, obesity, and diabetes mellitus; and hypercoagulation and hyperinflammation secondary to the viral infection.[7,51,52]

In two recent series of patients with severe COVID-19 who required ventilatory support, patients presented peripheral nerve involvement with a pattern corresponding to mononeuropathy multiplex; electroneurography studies showed axonal involvement in regions other than the typical entrapment sites, suggesting additional mechanisms other than mechanical compression.[53,54] Regarding this point, one case was reported of brachial plexopathy in a patient with COVID-19 and acute respiratory distress syndrome who was not placed in a prone position. The authors suggest a microvascular thrombotic mechanism as the underlying cause.[55]

Another possible (though rare) type of neuropathic involvement in patients with severe COVID-19 admitted to intensive care units is lumbosacral plexus neuropathy secondary to direct compression as a result of retroperitoneal haemorrhage, which may be associated with such systemic processes as coagulopathies, as well as traumatic or iatrogenic causes. The onset of these types of neuropathy in patients with severe COVID-19 was mostly attributed to the anticoagulant drugs used to prevent thrombotic events.[56]

Conclusion

Patients with recent history of COVID-19 often report symptoms suggestive of peripheral (somatic and/or autonomic) nervous system and muscular system dysfunction. However, with the exception of complications derived from ICU admission and the associated therapeutic measures, it is not always possible to measure dysfunction with the techniques typically available in clinical practice; we also lack understanding of the pathophysiology of these symptoms. When signs and symptoms are consistent with isolated or multiple mononeuropathy, it is essential to identify the possibility of increased risk in patients with COVID-19 of any level of severity. In other patients for whom objective data indicate peripheral polyneuropathy or myopathy, given the currently unclear pathophysiological relationship with COVID-19, we recommend following the usual approach to diagnosis and treatment in neuromuscular disorders clinics. Finally, some patients present sensory, dysautonomic, or motor syndromes with no objective data indicating neuromuscular involvement. Some of these symptoms share characteristics with such other disorders as chronic fatigue

syndrome and functional neurological disorders[57]; therefore, it is important to consider similar multidisciplinary therapeutic approaches. However, further research is needed to better understand the pathophysiology and natural history of these symptoms and to optimise the available treatments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2021.11.002.

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