

# Acute myopathic quadriplegia in patients with COVID-19 in the intensive care unit

Francesca Madia, MD, Barbara Merico, MD, Guido Primiano, MD, PhD, Salvatore Lucio Cutuli, MD, Gennaro De Pascale, MD, and Serenella Servidei, MD

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## Correspondence

Dr. Servidei  
serenella.servidei@unicatt.it

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It is well known that the spectrum of SARS-CoV-2 infection ranges from asymptomatic or mildly symptomatic patients to rapidly progressive, acute respiratory distress syndrome (ARDS) and death. Although various reports indicated the presence of myalgia in 44%–70% and increased creatine kinase (CK) in about 33% of hospitalized patients,<sup>1</sup> or <skeletal muscle injury> (increased CK and myalgia) in 23%,<sup>2</sup> the characterization of neuromuscular involvement is still unsatisfactory, and no electrophysiologic studies have been performed. Very recently, patients who developed the Guillain-Barré syndrome (GBS) in the course of coronavirus disease 2019 (COVID-19) have been described.<sup>3</sup> In the past literature, there were a few reports of neuromuscular involvement in association with other beta-coronavirus, including critical illness myopathy (CIM) or polyneuropathy.<sup>1,4</sup> Moreover, myopathic changes, as fiber atrophy or necrosis, have been reported in postmortem muscle samples of 8 patients who died of SARS (severe acute respiratory syndrome) due to SARS-CoV infection.<sup>4</sup>

## Patients

In the intensive care unit (ICU), we evaluated 6 ventilator-dependent SARS-CoV-2–confirmed patients for acute flaccid quadriplegia, which was noticed in attempting to lighten sedation and mechanical ventilation support. The age of the patients, 5 men and 1 woman, ranged from 51 to 72 years. In all patients, neurologically normal individuals, symptoms at the onset were fever and dyspnea rapidly evolving in ARDS requiring orotracheal intubation (OTI). Other comorbidities were myelofibrosis on therapy with low dose (12.5 mg) of prednisone (patient 2), insulin resistance (patient 4), and insulin-dependent diabetes and blood hypertension (patient 6). All 6 had pneumonia with characteristic bilateral patchy ground-glass opacities and interstitial changes and various superimposed infections or sepsis. Therapies, including specific COVID-19 protocols and treatments of complications, are listed in the table. All had hydroxychloroquine and enoxaparin since the beginning of symptoms. Time from the onset of COVID-19 manifestations and OTI was 6–14 days and from OTI and electrophysiologic studies 6–14 days (table). The neurologic examination in all 6 patients showed preserved extraocular, mimic and tongue muscles, flaccid quadriplegia with possibilities of little distal movements of the hands, no sensory abnormalities, retained but weak deep tendon reflexes. Neurophysiologic studies that included EMG and motor and sensory electroneurography (ENG) demonstrated in all subjects (1) myopathic abnormalities with fibrillation potentials and rapid recruitment of small, polyphasic motor units in deltoid or biceps, quadriceps, and tibial anterior, (2) reduced compound muscle action potential amplitude (below 40%–80% of normal) with markedly prolonged duration (table), (3) normal sensory nerve action potential amplitudes (table), (4) normal F wave (table), (5) absence of demyelinating features, and (6) normal repetitive motor nerve stimulation (4/4 patients). CK, normal or mildly elevated, with the highest level of 1274 UI/L in patient 4, decreased to normal or low-normal values in the course of the disease. All subjects had low serum proteins and elevated levels of C-reactive protein, D-dimer, and IL-6 (table). All patients were put on diet

From the UOC Neurofisiopatologia (F.M., B.M., G.P., S.S.), Fondazione Policlinico Universitario A. Gemelli IRCCS; Dipartimento di Scienze dell'Emergenza (S.L.C., G.D.P.), Anestesiologiche e della Rianimazione, Fondazione Policlinico Universitario A. Gemelli IRCCS; and Dipartimento Universitario di Neuroscienze (S.S.), Università Cattolica del Sacro Cuore, Rome, Italy.

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**Table** Clinical, laboratory, and electrophysiologic findings in 6 patients with SARS-CoV-2 with flaccid quadriplegia

| Pt | Age | Sex | Time from the onset of symptoms to OTI/time from OTI to ENG/EMG | CK (UI/L) max/last value | CRP mg/L max value | IL-6 ng/mL max value | D-dimer ng/mL max value | Treatment  | Motor nerve conduction studies <sup>a</sup><br>Proximal/distal amplitude<br>Conduction velocity   | Antidromic sensory nerve conduction studies <sup>a</sup>   |
|----|-----|-----|---|--------------------------|--------------------|----------------------|-------------------------|--|---|--|
| 1  | 51  | M   | 11/6 d  | 116/33                   | 155.1              | 18.4                 | 7,628                   | Levofloxacin, linezolid, oxacillin, piperacillin/tazobactam, darunavir/ritonavir, hydroxychloroquine, tocilizumab, and enoxaparin  | Peroneal nerve: DML 4.7 ms, CMAP: 0.4/0.3 mV, 40 m/s, mean CMAP duration 20.2 ms<br>Tibial nerve: DML 4.0 ms, CMAP: 2.7 mV, F wave: 55.7 ms, Mean CMAP duration 18.7 ms | Superficial peroneal nerve: SCV 48 m/s, SNAP 3.9 $\mu$ V.<br>Radial nerve: SCV 49 m/s, SNAP 12.3 $\mu$ V |
| 2  | 70  | M   | 6/9 d   | 500/167                  | 363.9              | 5,402.2              | 4,361                   | Linezolid, piperacillin/tazobactam, lopinavir/ritonavir, hydroxychloroquine, tocilizumab, and enoxaparin   | Peroneal nerve: DML 4.8 ms, CMAP: 0.3/0.3 mV, 40 m/s, Mean CMAP duration 18.3 ms  | NA <sup>b</sup>  |
| 3  | 53  | M   | 12/8 d  | 1,274/89                 | 33                 | 95.6                 | 5,238                   | Azithromycin, ceftriaxone, levofloxacin, linezolid, vancomycin, amikacin, meropenem, lopinavir/ritonavir, darunavir/ritonavir, endovenous corticosteroids, hydroxychloroquine, tocilizumab, and enoxaparin | Peroneal nerve: DML 4.7 ms, CMAP: 0.5/0.4 mV, 41 m/s, Mean CMAP duration 14.2 ms<br>Tibial nerve: DML 4.0 ms, CMAP: 3.6 mV, F wave: 60 ms, mean CMAP duration 19.1 ms   | Superficial peroneal nerve: SCV 48 m/s, SNAP 4.7 $\mu$ V   |
| 4  | 72  | M   | 14/10 d   | 55/17                    | 100.1              | 32.2                 | 3,286                   | Azithromycin, doxycycline, darunavir/ritonavir, endovenous corticosteroids, hydroxychloroquine, sarilumab, and enoxaparin  | Tibial nerve: DML 4.5 ms, CMAP: 6.8 mV, F wave: 54.4 ms, mean CMAP duration 20.2 ms. Ulnar nerve: DML 2.9 ms, CMAP: 1.9/1.5 mV, 49 m/s; mean CMAP duration 14.2 ms      | Ulnar nerve: SCV 50 m/s, SNAP 1.9 $\mu$ V  |
| 5  | 52  | M   | 14/10 d   | 133/111                  | 256.1              | 82.9                 | 6,408                   | Linezolid, imipenem, amoxicillin, darunavir/ritonavir, endovenous corticosteroids, hydroxychloroquine, tocilizumab, and enoxaparin   | Median nerve: DML 3.1 ms, CMAP: 3.7/3.5 mV, 46 m/s<br>F wave: 28.9 ms, mean CMAP duration 14.9 ms   | Median nerve: SCV 59 m/s, SNAP 11.9 $\mu$ V  |
| 6  | 68  | F   | 7/14 d  | 203/70                   | 196.8              | 123.9                | 2076                    | Azithromycin, ceftriaxone, darunavir/ritonavir, hydroxychloroquine, sarilumab, and enoxaparin  | Median nerve: DML 4.2 ms, CMAP: 3.8/3.7 mV, 45 m/s<br>F wave: 28.8, mean CMAP duration 18.1 ms  | Radial nerve: SCV 47 m/s, SNAP 6.3 $\mu$ V   |

Abbreviations: CK = creatine kinase; CMAP = compound muscle action potential; CRPP = C-reactive protein; DML = distal motor latency; ENG = electro-neurography; F wave = mean F-wave latency; Max = maximum; MCV = motor conduction velocity; NA = not available. OTI = orotracheal intubation; Pt = patient; SCV = sensory conduction velocity; SNAP = sensory nerve action potential.

Normal nerve conduction study values in our laboratory: median nerve, CMAP  $\geq$ 4–5 mV, DML  $\leq$ 4 ms, and MCV  $\geq$ 45 m/s; ulnar nerve, CMAP  $\geq$ 6 mV, DML  $<$ 3 ms, and MCV  $\geq$ 46 m/s; tibial nerve, CMAP  $\geq$ 5 mV and DML  $\leq$ 5 ms; peroneal nerve, CMAP  $\geq$ 2 mV, DML  $\leq$ 5 ms, and MCV  $>$ 39 m/s; radial nerve, SNAP  $\geq$ 5  $\mu$ V and SCV  $\geq$ 45 m/s; superficial peroneal nerve, SNAP  $\geq$ 5  $\mu$ V and SCV  $\geq$ 40 m/s; nerve F-wave cutoff was corrected for the height: median nerve, 150 cm  $\leq$ 25 ms, 160 cm  $\leq$ 27 ms, 170 cm  $\leq$ 29 ms, 180 cm  $\leq$ 30 ms, and 190 cm  $\leq$ 31 ms; tibial nerve, 150 cm  $\leq$ 44 ms, 160 cm  $\leq$ 48 ms, 170 cm  $\leq$ 53 ms, 180 cm  $\leq$ 58 ms, and 190 cm  $\leq$ 60 ms. Mean age of controls was 52  $\pm$  18 years (range 8–94 years). Control mean CMAP duration: peroneal nerve 5.5 ms, tibial nerve 5.4 ms, median nerve 5.4 ms, and ulnar nerve 6.0 ms.

Normal laboratory values: CK 30–170 UI/L, CRP  $<$ 5 mg/L, IL-6  $<$ 4.4 ng/mL, and D-dimer  $<$ 500 ng/mL.

<sup>a</sup> The neurophysiologic protocol variability is due to the clinical condition (i.e., edema and venous/arterial access).

<sup>b</sup> Due to environmental artifacts.

with high content of proteins and vitamins. Patient 2, with the highest value of IL-6 (5,402 ng/mL), died shortly after of intractable sepsis. Neurologic examination in the other 5 patients, 14 to 20 days from the first examination, showed a

clear improvement of muscular deficit. All of them are disconnected from the ventilator and capable to move and use their hands; 4/5 patients were able to sit unaided, and 1 was able to stand with aid.

## Discussion

Differential diagnosis of flaccid quadriplegia includes GBS, critical illness neuropathy and/or myopathy, and toxic myopathy. However, on the bases of EMG/ENG studies, clinical features with preserved face expression and ocular movements and the favorable outcome of muscle weakness, a diagnosis of CIM appears the most likely. Moreover, CIM major risk factors are severe respiratory distress, systemic inflammatory response, sepsis, hyperglycemia, steroids, and neuromuscular blockade,<sup>5</sup> factors that are mostly present in these patients. Although episodes of rhabdomyolysis have been reported during treatment with lopinavir/ritonavir in combination with a statin in HIV,<sup>1</sup> a toxic myopathy is instead unlikely as none of our patients were taking statins, and there was no evidence of acute myonecrosis with CK, which decreased in a few days.

By contrast, a direct effect of the virus on the muscle cannot be excluded. The mechanism of spreading, similarly to SARS-CoV, probably relies in SARS-CoV-2 ability to enter into the cells that express the angiotensin-converting enzyme 2 (ACE2) receptors.<sup>6</sup> Of interest, ACE2 is expressed in muscle and involved in the pathways implicated on insulin resistance, myoatrophy, and fibrosis.<sup>7</sup> Although SARS-CoV has not been found in the postmortem skeletal muscles showing features compatible with CIM from 2 patients who died of SARS, SARS-CoV-2 seems to have much higher affinity to ACE2 than SARS-CoV, and a direct insult of the virus cannot be ruled out. Alternatively, muscle involvement could be the result of immune-mediated damage in the contest of the hyperinflammation typical of the more advanced phases of COVID-19.

Whatever the mechanism, muscle weakness may contribute to prolonged mechanical ventilation and ventilator wean failure. CIM is a relatively frequent complication in ICU<sup>5</sup> maybe still under recognized in the setting of patients with COVID-19 for the overwhelming severe systemic manifestations and mortality. This is just a tile in the complex clinical pictures of SARS-CoV-2 infection but warrants further and more systemic studies to ensure the best possible approach to these patients.

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## Appendix Authors

| Name                              | Location   | Contribution  |
|-----------------------------------|--|---|
| <b>Francesca Madia, MD</b>        | Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy | Designed and conceptualized the study and analyzed the data   |
| <b>Barbara Merico, MD</b>         | Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy | Major role in the acquisition of data and revised the manuscript for intellectual content   |
| <b>Guido Primiano, MD, PhD</b>    | Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy | Major role in the acquisition of data and revised the manuscript for intellectual content   |
| <b>Salvatore Lucio Cutuli, MD</b> | Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy | Major role in the acquisition of data   |
| <b>Gennaro De Pascale, MD</b>     | Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy | Major role in the acquisition of data   |
| <b>Serenella Servidei, MD</b>     | Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy | Designed and conceptualized the study; analyzed the data; revised the manuscript for intellectual content; and drafted the manuscript |

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