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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Neuromuscular involvement in COVID-19 critically ill patients

Lidia Cabañes-Martínez a,e, Marta Villadóniga a, Liliana González-Rodríguez a, Lesly Araque a, Alba Díaz-Cid a, Ignacio Ruz-Caracuel b,f, Héctor Pian b, Susana Sánchez-Alonso c, Samira Fanjul d, Marta del Álamo e, Ignacio Regidor a

a Clinical Neurophysiology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain
b Pathology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain
c Intensive Care Unit, Hospital Universitario Ramón y Cajal, Madrid, Spain
d Neurology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain
e Neurosurgery Department, Hospital Universitario Ramón y Cajal, Madrid, Spain
f Research Group in Muscle Regeneration, University of Cordoba, Cordoba, Spain

Article info

Article history:
Accepted 30 September 2020
Available online 15 October 2020

Keywords:
Critical illness neuromyopathy
COVID-19
Neurophysiology
Neuromuscular disorders
Pandemic

Highlights

- Many COVID-19 patients require ICU stay which can result in neuromuscular damage.
- We describe a series of patients with the diagnosis of ICU acquired weakness.
- Neurophysiology plays an essential role in the diagnosis of these patients.

Abstract

Objective: Coronavirus disease 2019 (COVID-19) has a high incidence of intensive care admittance due to the severe acute respiratory syndrome (SARS). Intensive care unit (ICU)-acquired weakness (ICUAW) is a common complication of ICU patients consisting of symmetric and generalised weakness. The aim of this study was to determine the presence of myopathy, neuropathy or both in ICU patients affected by COVID-19 and whether ICUAW associated with COVID-19 differs from other aetiologies.

Methods: Twelve SARS CoV-2 positive patients referred with the suspicion of critical illness myopathy (CIM) or polyneuropathy (CIP) were included between March and May 2020. Nerve conduction and concentric needle electromyography were performed in all patients while admitted to the hospital. Muscle biopsies were obtained in three patients.

Results: Four patients presented signs of a sensory-motor axonal polyneuropathy and seven patients showed signs of myopathy. One muscle biopsy showed scattered necrotic and regenerative fibres without inflammatory signs. The other two biopsies showed non-specific myopathic findings.

Conclusions: We have not found any distinctive features in the studies of the ICU patients affected by SARS-CoV-2 infection.

Significance: Further studies are needed to determine whether COVID-19-related CIM/CIP has different features from other aetiologies. Neurophysiological studies are essential in the diagnosis of these patients.

© 2020 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. All rights reserved.

1. Introduction

Currently, coronavirus disease 2019 (COVID-19), caused by the SARS CoV-2, has spread worldwide, with more than 19 million cases globally, including 314,362 cases in Spain (WHO situation report 204). The overall incidence of critically ill patients due to the severe acute respiratory syndrome (SARS) caused by this virus is unknown; reports from the Wuhan region estimate an incidence of 17% (Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention, 2020), whereas preliminary results from Spain estimate an incidence around 8% (Casas-Rojo et al., 2020).

https://doi.org/10.1016/j.clinph.2020.09.017
1388-2457/© 2020 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. All rights reserved.
Intensive care unit (ICU)-acquired weakness (ICUAW) was first described in the early 80s (Bolton, 2010), and it is a common complication in critically ill patients. It causes acquired weakness affecting limb and respiratory muscles, causing difficulty in weaning patients from the ventilator. It results in a prolonged stay in the ICU and an increase in morbidity and mortality (Nanas et al., 2008; Latronico and Bolton, 2011). The term ICUAW comprises critical illness myopathy (CIM), critical illness polyneuropathy (CIP), and a combination of both (CIMP). Muscle dysfunction is thought to be the primary cause of ICUAW although in many cases, both neuropathy and myopathy coexist (or it is not possible to determine which is the primary dysfunction) (de Carvalho, 2020). CIM is a primary myopathy and its pathophysiology is not yet well known. Some risk factors have been identified, such as premorbid health status, duration of mechanical ventilation and severity of the acute disease. Its diagnosis is based on clinical criteria, electrophysiological studies (nerve conduction studies (NCS) and electromyography (EMG) and muscle biopsy (Z’Gragggen and Tankisi, 2020). CIP is a symmetrical length-dependent sensory-motor axonal polyneuropathy. The exact mechanisms are not well understood. For its diagnosis, clinical criteria and electrophysiological studies are needed (Tankisi et al., 2020a). CIM has a better prognosis than CIP according to published studies (Koch et al., 2014).

The primary objective of our study is to determine the presence of myopathy, neuropathy or both in ICU patients affected by COVID-19 in our centre. A secondary objective is to determine whether ICUAW associated with COVID-19 differs from other aetiologies.

2. Materials and methods

During the first outbreak of the pandemic in Madrid (Spain), between 31st March 2020 and 18th May 2020, 3030 patients with the suspected diagnosis of SARS CoV-2 infection were hospitalised in our centre, a tertiary-level hospital. In this period, 12 patients from a total of 225 COVID patients treated in the ICU were referred to the Clinical Neurophysiology Department, with a suspicion of ICUAW due to a clinical picture of generalised weakness associated in some cases with difficulty in weaning from the ventilator. We have conducted a retrospective single-centre study including clinical data, neurophysiological studies and muscle biopsies. The study has been approved by the Clinical Research Ethics Committee of our Hospital.

Neurophysiological studies were performed in all of the patients, as well as muscle biopsies when possible. The only exclusion criteria applied was the presence of a pre-existing neuromuscular disorder.

2.1. Neurophysiological protocol

Neurophysiological studies were performed mostly in the ICU, except in four cases in which the studies were performed in the hospitalisation ward.

The neurophysiological study consisted in motor and sensory nerve conduction studies and concentric needle electromyography of different muscles depending on the patient’s clinical presentation (proximal and/or distal muscles of both upper and lower limbs). All studies were performed using a Keypoint.Net v2.33 EMG equipment (Dantec, Skovlunde, Denmark).

NCS: We studied motor and sensory conductions of the upper (median) and lower limbs (peroneal, posterior tibial and sural nerves) in every patient. Surface stimulation was always performed. Surface recording was carried out whenever possible with disposable pre-gelled surface electrodes (Ag/AgCl) (Ambu Neuroline 715) and monopolar needles ( uninsulated stained steel Neuroline subdermal) were used only when peripheral oedema was important. Sensory NCS were conducted with antidromic stimulation.

Distal motor latency, motor and sensory conduction velocities, compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitude and duration were measured. F waves of posterior tibial nerve were also performed.

EMG: Disposable concentric needles (Dantec DCN) were used. Distal and proximal muscles were explored, most commonly first dorsal interosseous and posterior deltoid muscles in the upper limb; and quadriceps (vastus lateralis) and tibialis anterior muscles in the lower limb. In addition to the presence or absence of spontaneous activity, quantitative EMG was performed when possible: mean amplitude and duration of motor unit potentials (MUP) were measured, as well as the percentage of polyphasic potentials. The recruitment pattern was also evaluated in those cases where the clinical situation of the patient allowed it.

2.2. Muscle biopsy

Skeletal muscle from three patients was biopsied (one tibialis anterior and two quadriceps). The election of the muscle to study was made taking into account the degree of muscular involvement according to the EMG. In all cases, an open muscle biopsy procedure was followed, and specimens were immediately transferred to the Pathology Department. Biopsies were divided in two fragments. One fragment was embedded in OCT (Tissue-Tek ™, Miles INC) and flash-frozen in isopentane cooled with liquid nitrogen. This fragment was evaluated using standard histological, histochemical and immunohistochemical techniques (Dubowitz et al. 2013). The following antibodies were used: HLA (clone W6/32, Dako®, Glostrup, Denmark) and C5b9 (clone aE11, Dako®, Glostrup, Denmark). The smaller fragment was formalin-fixed, and paraffin embedded.

3. Results

The average age of the 12 patients was 65 years (52–75). 10 were men (83.3%) and two were women (16.7%). The length of their stay in the ICU prior to the performance of the neurophysiological study and biopsy was variable, ranging between 12 and 49 days, with a mean of 24 days. The clinical evolution was variable, with seven patients being discharged from the ICU and five of them deceased. Table 1 summarises the clinical data of the patients.

All the patients had at least one positive polymerase chain reaction (PCR) confirming a SARS CoV-2 infection. They all presented with weakness in upper and lower limbs and laboratory findings such as elevated creatin kinase (CK) levels, elevated D-dimer and lymphopenia. They all received multiple pharmacological therapies (antiretrovirals, neuromuscular blockers, corticosteroids, and antibiotics). None of the patients had a previously diagnosed neuromuscular disorder.

3.1. Neurophysiological study

The neurophysiological study was normal in one of the cases (case 9).

The study was pathological in the 11 remaining patients:

In four patients (5, 7, 8 and 11), we found a decreased amplitude of both motor and sensory evoked potentials with normal duration and predominance in lower limbs (Fig. 1). Needle EMG in proximal muscles showed either absence or presence of very mild spontaneous activity, without MUP abnormalities. These four studies...
| Case | Sex | Age | Symptoms | Days in ICU | Treatments | CK levels |
|------|-----|-----|----------|-------------|------------|-----------|
| 1    | F   | 75  | Generalised muscular weakness | 12 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Ceftriaxone, meropenem, linezolid,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine,
|      |     |     |                       |   | tocilizumab | Maximum peak: 1321 μmol/l,
|      |     |     |                       |   | Progressive normalization in 6 days | |
| 2    | M   | 52  | Generalised muscular weakness | 16 | Cisatracurium, Methylprednisolone,
|      |     |     |                       |   | Vancomycin, piperacillin/tazobactam,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine,
|      |     |     |                       |   | tocilizumab | Maximum peak: 1544 μmol/l,
|      |     |     |                       |   | Progressive normalization in 13 days | |
| 3    | M   | 66  | Generalised muscular weakness | 21 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Azithromycin, piperacillin/tazobactam,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine,
|      |     |     |                       |   | tocilizumab | Maximum peak: 314 μmol/l,
|      |     |     |                       |   | Progressive normalization in 6 days | Normal range |
| 4    | M   | 71  | Generalised muscular weakness | 29 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Ceftriaxone, piperacillin/tazobactam,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine | |
| 5    | M   | 75  | Generalised muscular weakness | 30 | Rocuronium,
|      |     |     | (distal) Failure to wean from ventilator |   | Ceftriaxone, azithromycin, ceftaroline, daptomycin, meropenem, linezolid,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine | Maximum peak: 181 μmol/l,
|      |     |     |                       |   | Progressive normalization in 1 day | |
| 6    | F   | 74  | Generalised muscular weakness | 30 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Azithromycin, moxifloxacin, ceftaroline,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine | Maximum peak: 314 μmol/l,
|      |     |     |                       |   | Progressive normalization in 5 days | Normal range |
| 7    | M   | 61  | Generalised muscular weakness | 21 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Azithromycin, ceftriaxone,
|      |     |     |                       |   | Cisatracurium, Methylprednisolone,
|      |     |     |                       |   | Ceftriaxone, meropenem, azithromycin, vancomycin, ceftolozane/tazobactam,
|      |     |     |                       |   | Cefazidime/avibactam,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine | Maximum peak: 385 μmol/l,
|      |     |     |                       |   | Progressive normalization in 4 days | Normal range |
| 8    | M   | 66  | Mild generalised weakness | 24 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Hydrocortisone,
|      |     |     |                       |   | Piperacillin/tazobactam, ceftriaxone, azithromycin, linezold.
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine | Maximum peak: 1071 μmol/l,
|      |     |     |                       |   | Progressive normalization in 3 days | |
| 9    | M   | 60  | Generalised muscular weakness | 16 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Hydrocortisone,
|      |     |     |                       |   | Piperacillin/tazobactam, ceftriaxone, azithromycin, linezold.
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine | Maximum peak: 528 μmol/l,
|      |     |     |                       |   | Progressive normalization in 12 days | 
| 10   | M   | 58  | Generalised muscular weakness | 27 | Cisatracurium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Piperacillin/tazobactam, ceftriaxone, meropenem, azithromycin, vancomycin,
|      |     |     |                       |   | linezold, amikacin,
|      |     |     |                       |   | Lopinavir/ritonavir, hydroxychloroquine | Maximum peak: 3228 μmol/l,
|      |     |     |                       |   | Progressive normalization in 23 days | |
| 11   | M   | 63  | Mild generalised weakness | 23 | Rocuronium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Tigecycline, piperacillin/tazobactam, erythromycin, clindamycin, levofloxacin,
|      |     |     |                       |   | linezold, amphotericin B, metronidazole,
|      |     |     |                       |   | hydroxychloroquine | |
| 12   | M   | 52  | Generalised muscular weakness | 49 | Rocuronium, Methylprednisolone,
|      |     |     | Failure to wean from ventilator |   | Piperacillin/tazobactam, levofloxacin, linezold, ceftriaxone, amikacin, voriconazole,
|      |     |     |                       |   | ceftazidime/avibactam, metronidazole, trimethoprim/sulfamethoxazole,
|      |     |     |                       |   | Lopinavir/ritonavir, tocilizumab | |

**Fig. 1.** Patient 7: Right peroneal nerve compound muscle action potential (CMAP) with normal distal motor latency, normal duration and decreased amplitude. Left sural nerve sensory nerve action potential (SNAP) with decreased amplitude.
were concluded as having signs of a sensory-motor axonal polyneuropathy.

In seven patients (1, 2, 3, 4, 6, 10 and 12) we found some degree of EMG abnormalities. Abundant spontaneous activity was found in the needle EMG of these seven patients. In two studies (patients 3, 12), voluntary muscle activation was not possible due to patients’ clinical situation. In the remaining cases (patients 1, 2, 4, 6 and 10), short motor unit potentials were found, with decreased amplitude and duration, although in some muscles the mean values of duration and amplitude were normal. All of the NCS studies showed a preservation of sensory nerve action potentials. Three of them (patients 1, 3 and 4) showed decreased amplitude of CMAPs in some nerves accompanied by an increased duration. F wave latency was within normal limits except in two cases, where the absence of the F wave of both posterior tibial nerves was noted. Repetitive nerve stimulation showed no abnormalities in any of the cases. All of these studies were concluded as having electromyographic signs of myopathy.

Tables 2 and 3 summarise the NCS and EMG data.

3.2. Creatine kinase levels

CK blood levels were elevated in nine patients (75%). Most of the determinations were not very high except in three patients (patients 4, 7 and 9) which presented levels above 1.000 μmol/l (normal range 45–100 μmol/l), and even in those cases CK levels returned to normal values within days. In most patients the highest CK levels were around 300 μmol/l.

3.3. Muscle biopsy

Case 3 muscle biopsy showed scattered necrotic and regenerative fibres in the absence of inflammatory infiltrates. Most of the fibres were in a similar phase of the degenerative-regenerative process and there was no increase in fibres showing internal nuclei. Oxidative histochemical techniques did not show any alterations apart from changes related to degeneration-regeneration. Muscle fascicles retained its mosaic pattern with ATPases techniques. Vessels did not have any alterations; no inflammation or thrombi were found. The other two skeletal muscle biopsies (cases 1 & 2) showed non-specific findings consisting on very occasional atrophic and regenerative fibres. None of the biopsies stained for HLA or C5b9 (Fig. 3).

4. Discussion:

We present a series of cases of ICUAW as a consequence of COVID-19, to our knowledge the first series published so far. COVID-19 has a wide variety of clinical presentations, being acute respiratory distress syndrome one of the most severe presentation (Wu et al., 2020). The mortality rate of the disease is 2.7–3.4% (San-Juan et al., 2020), with many patients requiring ICU treatment (Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention, 2020). During the spring of 2020, more than 3000 COVID-19 patients were admitted to our hospital, with more than 200 admitted to the ICU.

The complete neurological involvement of COVID-19 is yet to be described. Studies so far suggest that it might be major, not only in the number of patients affected but also in the severity of the disease. However, neurological sequelae of this disease are not only derived from the potential direct damage of the virus to the nervous system (Helms et al., 2020; Jimenez-Ruiz et al., 2020; Mao et al., 2020) but also, as described in our patients, from the severity of the systemic disease itself.

COVID-19 can result in severe respiratory diseases such as acute respiratory distress syndrome, which leads patients to the ICU or even death (Chen et al., 2020). In the previous SARS-CoV outbreak in 2002, different neurological manifestations were described (Tsai et al., 2003). We present a series of cases of ICUAW as a consequence of COVID-19, to our knowledge the first series published so far.
| NERVE | PATIENT 1 | PATIENT 2 | PATIENT 3 | PATIENT 4 | PATIENT 5 | PATIENT 6 |
|-------|----------|----------|----------|----------|----------|----------|
|       | A    | V   | L   | D   | A    | V   | L   | D   | A    | V   | L   | D   | A    | V   | L   | D   | A    | V   | L   | D   | A    | V   | L   | D   |
| Sural |       |       |       |      |       |       |       |      |       |       |       |       |      |       |       |      |       |       |       |       |       |       |       |       |       |
| -      |       |       |       |      |       |       |       |      |       |       |       |       |      |       |       |      |       |       |       |       |       |       |       |       |       |
| Right  | 15.4  | 49.8 | 2.81 | 1.22 | 5.60  | 52.8 | 2.65 | 2.50 | 11.3  | 57.6 | 1.65 | 1.71 | 8.50  | 39.2 | 3.85 | 2.10 | 2.0   | 55.3 | 2.17 | 1.39 | 7.90  | 48.1 | 2.08 | 2.10 |
| Left   | 8.90  | 48.3 | 2.90 | 1.63 | 14.0  | 38.2 | 3.93 | 1.81 | 15.1  | 62.5 | 2.08 | 1.40 | 8.30  | 58.6 | 2.39 | 1.51 | 2.9   | 56.8 | 2.20 | 1.39 | 25.4  | 43.0 | 2.56 | 1.77 |
| R peroneal |       |       |       |      |       |       |       |      |       |       |       |       |      |       |       |      |       |       |       |       |       |       |       |       |       |
| Distal | 0.72  | 3.97 | 6.38 | 7.40 | 0.15  | 4.10 | 3.60 | 4.08 | 0.70  | 5.68 | 4.80 | 4.08 | 0.70  | 3.97 | 6.38 | 7.40 | 0.15  | 4.10 | 3.60 | 4.08 | 0.70  | 5.68 | 4.80 | 4.08 |
| Proximal | 0.54 | 45.2 | 10.5 | 10.7 | 3.50 | 52.5 | 15.0 | 8.20 | 0.16 | 48.3 | 11.3 | 8.00 | 0.50 | 58.3 | 17.1 | 8.10 | --   | --   | --   | --   | --   | --   | --   |
| L peroneal |       |       |       |      |       |       |       |      |       |       |       |       |      |       |       |      |       |       |       |       |       |       |       |       |       |
| Distal | 1.22  | 3.73 | 9.20 | 4.08 | 4.30  | 4.69 | 11.3 | 4.00 | 0.40  | 5.85 | 16.6 | 4.20 | 3.90  | 10.3 | 6.20 | 3.20 | 10.3 | 6.20 | 3.20 | 10.3 | 6.20 | 3.20 | 10.3 |
| Proximal | 0.95 | 45.0 | 10.4 | 10.2 | 3.50 | 55.9 | 14.8 | 8.10 | 0.10 | 50.8 | 13.3 | 12.8 | --   | --   | --   | --   | --   | --   | --   | --   | --   | --   | --   |
| R tibialis |       |       |       |      |       |       |       |      |       |       |       |       |      |       |       |      |       |       |       |       |       |       |       |       |       |
| Distal | 5.0   | 6.30 | 9.20 | 8.20 | 4.0   | 7.30 | 6.60 | 4.00 | 0.40  | 5.85 | 16.6 | 4.20 | 3.90  | 10.3 | 6.20 | 3.20 | 10.3 | 6.20 | 3.20 | 10.3 | 6.20 | 3.20 | 10.3 |
| Proximal | 4.00 | 45.0 | 10.4 | 10.2 | 3.50 | 55.9 | 14.8 | 8.10 | 0.10 | 50.8 | 13.3 | 12.8 | --   | --   | --   | --   | --   | --   | --   | --   | --   | --   |
| L tibialis |       |       |       |      |       |       |       |      |       |       |       |       |      |       |       |      |       |       |       |       |       |       |       |       |       |
| Distal | 5.30  | 4.30 | 6.00 | 7.00 | 2.80  | 4.00 | 14.2 | 9.50 | 2.50  | 55.0 | 11.1 | 9.40 | 3.60  | 49.5 | 14.7 | 10.7 | 0.49  | 42.9 | 13.7 | 12.8 | 4.10  | 42.0 | 13.2 | 6.80 |
| Proximal | 4.70 | 43.0 | 12.0 | 7.00 | 2.80  | 4.00 | 14.2 | 9.50 | 2.50  | 55.0 | 11.1 | 9.40 | 3.60  | 49.5 | 14.7 | 10.7 | 0.49  | 42.9 | 13.7 | 12.8 | 4.10  | 42.0 | 13.2 | 6.80 |
| F RESPONSE | Normal | Normal | Normal | Normal | Absent | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal |

NCS: Nerve Conduction Studies; R: Right; L: Left; A: Amplitude (Motor: mV, Sensory: μV); V: Velocity (m/s); L: Latency (ms); D: Duration (ms); --: No response.
et al., 2005), including neuromuscular involvement. Tsai et al. reported four patients with probable SARS secondary to coronavirus who developed neuromuscular problems after the onset of the symptoms, with a final diagnosis of probable CIP (Tsai et al., 2004). The exact proportion of SARS requiring ICU treatment is not reported. In our work, we describe 11 patients with a clinical and neurophysiological diagnosis of CIM or CIP, of a total of 225 patients treated in the ICU. However, for different reasons, it is not possible to calculate the exact incidence of the presence of neuropathy or myopathy. Due to the severity of the disease, it is conceivable that a number of patients died without a diagnostic study. Moreover, due to the infectious nature of the disease, non-essential studies were delayed or even cancelled. Besides, at the peak of the outbreak, resources were limited and the medical staff of many departments, Clinical Neurophysiology included, were relocated to the general care of COVID-19 patients and therefore, fewer neurophysiological studies were performed during that period. For the same reasons, it is difficult to pinpoint a well-defined time interval between the acute respiratory distress syndrome caused by COVID-19 and the appearance of neurological symptoms, since in the vast majority of cases it is not possible to determine the exact onset of tetraparesis. The time between the description of weakness and the performance of the neurophysiological study is very variable as well.

The term ICUAW describes a neuromuscular dysfunction consisting of generalised and symmetric weakness affecting limbs and usually respiratory muscles (Stevens et al., 2009; Vanhorebeek et al., 2020). It appears in patients with multiple organ failure associated with sepsis and systemic inflammatory response, especially in those patients ventilated for long periods of time (Hermans and Van den Berghe, 2015). It is essential for the diagnosis that no other explanation for the neuromuscular dysfunction exists, apart from the critical illness and its treatments (Stevens et al., 2009; Vanhorebeek et al., 2020). All the patients from our series suffered from a severe form of acute respiratory distress syndrome caused by SARS-CoV-2, with long ICU stays (variable, but more than 12 days), and presented general weakness and/or difficulty to wean from the ventilator, which are typical symptoms of ICUAW. Their clinical records did not show any prior medical conditions which could explain their current neuromuscular symptoms.

We found signs of CIM or CIP in 11 of the 12 patients. Of these 11 patients, seven were diagnosed of critical illness myopathy (63.6%), and four of critical illness neuropathy (36.4%). None of the patients presented both signs of myopathy and neuropathy. It is known that in ICUAW membrane excitability is reduced (Friedrich et al., 2015). However, we have not performed electro-physiological tests to specifically measure membrane excitability.

|        | Patient 1               | Patient 2        | Patient 3               | Patient 4               | Patient 5               | Patient 6               |
|--------|-------------------------|------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Upper Limb |                         |                  |                         |                         |                         |                         |
| Proximal| SA: Abundant. PSW, FP   | No               | Abundant. PSW, FP       | Abundant. PSW, FP       | No                      | Few. FP                 |
| MUP    | A: ↓, D: ↓              | Normal           | No VM                   | No VM                   | Normal                  | No VM                   |
| IP     | Early recruitment       | Early recruitment | –                       | –                       | Normal                  | –                       |
| Distal | SA: Abundant. PSW, FP   | Abundant. PSW    | Abundant. PSW, FP       | Abundant. PSW, CRD      | –                       | Abundant. PSW, FP       |
| MUP    | A: ↓, D: ↓              | No VM            | No VM                   | No VM                   | –                       | No VM                   |
| IP     | Submaximal              | Submaximal       | –                       | –                       | –                       | –                       |
| Lower Limb |                       |                  |                         |                         |                         |                         |
| Proximal| SA: Moderate. PSW, FP   | Moderate. PSW    | Moderate. PSW           | Few. PSW                | No                      | No                      |
| MUP    | A: ↓, D: ↓              | Normal           | No VM                   | A: ↓, D: ↓              | Normal                  | A: ↓, D: ↓              |
| IP     | Submaximal              | Early recruitment| –                       | –                       | Normal                  | –                       |
| Distal | SA: Moderate. PSW, FP   | Few. FP          | Abundant. PSW, FP       | Abundant. PSW, FP       | –                       | Moderate. PSW           |
| MUP    | Normal                  | Normal           | No VM                   | Normal                  | –                       | No VM                   |
| IP     | Submaximal              | Normal           | –                       | –                       | –                       | –                       |

EMG: electromyography; SA: Spontaneous activity. PSW: positive sharp waves. FP: fibrillation potentials. CRD: complex repetitive discharges. MUP: motor unit potentials mean duration (D) and amplitude (A).

VM: voluntary movement. IP: interference pattern. –: not performed.
In our CIP patients, the diagnosis was made based on the low amplitude of CMAP and SNAP, but these findings may be also explained by this reduced excitability. Although EMG did not show specific myopathic changes in these patients (and the presence of spontaneous activity was taken as a sign of membrane dysfunction), some degree of primary muscle involvement cannot be completely ruled out.

An important finding in our COVID-19 series is that the degree of spontaneous activity was strikingly severe in the myopathy cases. We do not have a definite explanation for these findings; however, some causes may be taken into account. One of them might be the presence of potential risk factors for the appearance of myopathy, such as the use of corticosteroids, neuromuscular blocking drugs and some antibiotics. The association between these drugs and CIM is uncertain, as some reports suggest an increased incidence with these treatments (Larsson et al., 2000; De Jonghe et al., 2002; Garnacho-Montero et al., 2005; Vanhorebeek et al., 2020), but later studies have refuted this idea (Weber-Carstens et al., 2010). To this day, the exact relationship between the use of corticosteroids and neuromuscular blocking agents and CIM remains unclear. Another factor to take into account is the possible direct muscular damage caused by the SARS-CoV-2. Some viral infections can cause rhabdomyolysis, e.g. influenza virus (Yoshino et al., 2000) or HIV (Authier et al., 2005). Moreover, cases of rhabdomyolysis were reported in the 2003 SARS-CoV outbreak (Wang et al., 2003; Tsai et al., 2004). Nevertheless, direct muscular damage by the virus has not been proven, and no skeletal muscle lesions have been reported in autopsies apart from psosas haemorrhage (Polak et al., 2020).

Regarding pathology, skeletal muscle biopsies in our patients showed a non-specific degenerative-regenerative process. The fact that most of the degenerative-regenerative fibres were in the same phase, suggests that the etiological trigger acted during a short period of time close to the moment the biopsy was taken. Moreover, there was no increase in fibres with internal nuclei, a sign of a finished regenerative process. The absence of HLA or C5b9 immunostaining discarded an immune-mediated necrotising myopathy (Allenbach and Benveniste, 2018), that can show a close morphological pattern with hematoxylin-eosin. There were no morphological features of an established neurogenic process such as angulated or target fibres. Although signs of microvascular damage such as thrombi and endotheliitis have been described in many organs (Polak et al., 2020), vessels were intact in our skeletal muscle biopsies. These results support the diagnosis of CIM.

We have to admit that our study has some limitations. First, the number of patients in our series is limited, and a higher number of cases is necessary to draw stronger conclusions. In addition, the number of muscle biopsies in our study is low, and no nerve biopsies were performed. Finally, measurement of the myosin loss may be a more useful diagnostic tool than routine muscle biopsy for the diagnosis of CIM and it might correlate better with weakness (Larsson et al., 2000; Friedrich et al., 2015). Therefore, this technique should be considered in further studies.

Fig. 3. Skeletal muscle biopsy showing (A) scattered necrotic fibers (arrowhead) in the absence of inflammatory infiltrate (hematoxylin-eosin, 20x). (B) Higher magnification of two necrotic fibers being phagocyted by macrophages (H-E, 40x). (C) There were no thrombi or inflammatory infiltrates in the vessels (H-E, 40x). Also note the absence of angulated fibers. (D) There was no deposit of C5b9 by immunohistochemistry in non-necrotic fibers (C5b9, 20x).
To our knowledge, just one case of CIM secondary to COVID-19 has been reported so far (Tankisi et al., 2020b), in this case without muscle biopsy. The clinical picture and the neurophysiological studies in this report resemble the ones of our myopathy patients, and reinforce our results.

5. Conclusion

We have presented a series of 12 patients with confirmed COVID-19 and long stay in ICU out of whom 11 developed critical illness neuropathy or myopathy. Neurophysiological and pathological data agree with this diagnosis. We have not found any distinctive features of SARS-CoV-2 infection, but further studies are necessary, especially to determine whether COVID-19 related ICUAW has a similar prognosis.

We agree with the authors of the only previously reported case (Tankisi et al., 2020b), that, as many COVID-19 patients require long-term and intense ventilatory therapy, more cases of CIP, CIM or CIMP are expected in the future. The role of the neurophysiological and pathological studies has to be determined, particularly in exceptional situations where resources may be limited. In our opinion, NCS and EMG play an essential role in the diagnosis of these patients, and they should be considered at least in those cases in which the diagnosis is unclear.

Funding/financial support

No public funding or financial support was received by any of the authors of this manuscript regarding their participation in this work.

None of the authors have any personal or institutional financial interest in drugs, materials or devices described in this work.

Acknowledgements

We thank all the healthcare staff of the Intensive Care Units of our hospital for their excellent care and dedication to the patients during the COVID-19 pandemic. We also thank Dr. Gema de Blas for her continuous teaching and Dr. Martin for her assistance with the language review of the manuscript.

References

Allenbach Y, Benveniste O. Peculiar clinicopathological features of immune-mediated necrotizing myopathies. Curr Opin Rheumatol 2018;30:635–63.

Authier F-J, Charrot P, Gherardi RK. Skeletal muscle involvement in human immunodeficiency virus (HIV)-infected patients in the era of highly active antiretroviral therapy (HAART). Muscle Nerve 2005;32:247–60.

Bolton CF. The discovery of critical illness polymyopathy: a memoir. Can J Neurol Sci 2010;37:431–8.

de Carvalho M. Intensive care unit-acquired weakness: introductory notes. J Clin Neurophysiol 2020;37:195–6.

Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, Lumbreza-Bermajo C, Ramos-Rincón JM, Roy-Vallejo E, et al. Características clínicas de los pacientes hospitalizados con COVID-19 en España: resultados del Registro SEMI-COVID-19. Rev Clin Esp 2020 [published online ahead of print, 2020 Jul 19].

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;395:507–13.

De Jonghe B, Sharshar T, Lefaucheur J-P, Authier F-J, Durand-Zaleski I, Boussarar M, et al. Pareis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288:2859–67.

Dubowitz V, Sewry CA. Muscle biopsy: a practical approach: expert consult; Online and print. Elsevier Health Sciences; 2013.

Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 2020;41(14):145−51.

Friedrich O, Reid MB, Van den Berge G, Vanhorebeek I, Hermans G, Rich MM, et al. The sick and the weak: neuropaathies/myopathies in the critically ill. Physiol Rev 2015;95:1025−1055.

Garnacho-Montero J, Amaya-Villar R, García-Garmendía JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients*. Crit Care Med 2005;33:349–54.

Helms J, Kremser S, Merdji H, Clerc-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020;382:2268–70.

Hermans G, Van den Berge G. Critical review: intensive care unit acquired weakness. Crit Care 2015;19:274.

Jimenez-Ruiz A, Garcia-Grinshaw M, Ruiz-Sandoval JL. Neurological manifestations of COVID-19. Gac Med Mex 2020;156:257.

Koch S, Wollersheim T, Bierbrauer J, Haas K, Mörgeli R, Deja M, et al. Long-term recovery In critical illness myopathy is complete, contrary to polyneuromyopathy. Muscle Nerve 2014;50:431–6.

Larsson L, Liu X, Edström L, Zackrisson H, Argenti C, Schiaffino S. Acute quadriplegia and loss of muscle myosin in patients treated with nondepolarizing neuromuscular blocking agents and corticosteroids: mechanisms at the cellular and molecular levels. Crit Care Med 2008;36:34–45.

Latroonc N, Bolton C. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol 2011;10:931–41.

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;77:683–90.

Nanas S, Kritikos K, Angelopoulos E, Siafaka A, Tsikiris S, Poriazi M, et al. Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. Acta Neurol Scand 2008;118:175–81.

Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paasen J. A systematic review of pathological findings in COVID-19: a pathological timeline and possible mechanisms of disease progression. Med Pathol 2020. https://doi.org/10.1038/s41370-020-0603-3.

San Juan D, Jiménez CR, Camillii CX, de la Cruz Reyes LA, Galindo EGA, Barbosa GER, et al. Guidance for clinical neurophysiology examination throughout the COVID-19 pandemic. Latin American chapter of the IFCN task force – COVID-19. Clin Neurophysiol 2020;131:1589–98.

Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med 2009;37:5299−308.

Tankisi H, de Carvalho M, Z’Graggen WJ. Critical illness myopathy. J Clin Neurophysiol 2020;37:205–7.

Tankisi H, Tankisi A, Harbo T, Markvardsen LK, Andersen H, Pedersen TH. Critical illness myopathy as a consequence of Covid-19 infection. Clin Neurophysiol 2020;131:1931−2.

Tsai L-K, Hsieh S-T, Chang Y-C. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan 2005;14:113−9.

Tsai L-K, Hsieh S-T, Chao C-C, Chen Y-C, Lin Y-H, Chang S-C, et al. Neuromuscular disorders in severe acute respiratory syndrome. Arch Neurol 2004;61:1669–73.

Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med 2010;36:637–53.

Weber-Carstens S, Deja M, Koch S, Spranger J, Bubser F, Wernecke KD, et al. Risk factors in critical illness distres syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Int Med 2020;180:1−11.

Yoshino M, Suzuki S, Adachi K, Fukayama M, Inamatsu T. High incidence of acute myositis with type A influenza virus infection in the elderly. Int Med 2005;39:431−2.

Z’Graggen WJ, Tankisi H. Critical illness myopathy. J Clin Neurophysiol 2020;37:200−4.