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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Letter to the Editor

Comprehensive work-up is warranted for patients with severe COVID-19 and muscle weakness including respiratory muscles

With interest we read the article by Cabañes-Martínez et al. about 12 patients with COVID-19 and a negative history for neuromuscular disorders (NMDs), who developed muscle weakness and respiratory failure during hospitalization on the intensive care unit (ICU) for complications of the viral infection (Cabañes-Martínez et al., 2020). The authors found that 11 of these patients had critical ill neuropathy (CIN) or critical ill myopathy (CIM) (Cabañes-Martínez et al., 2020). It was concluded that the prevalence of CIN and CIM will increase with the increasing number of COVID-19 patients requiring ICU treatment and that nerve conduction studies (NCSs) and electromyography (EMG) will play crucial roles in the work-up of neuro-COVID (Cabañes-Martínez et al., 2020). We have the following comments and concerns.

The first shortcoming of the study is that the entire previous individual history of the 12 included patients was not provided. Knowing the individual history is crucial for truly excluding any cause of a primary or secondary NMD. Exclusion of previous cardiac and pulmonary disease is needed to assess if such disorders contributed to respiratory failure.

A second shortcoming is that the family history of each patient was not provided. Knowing the family history is worthwhile to exclude any genetic cause of a NMD. Since penetrance of primary NMDs varies greatly and since not each patient may be clinically but only subclinically affected, it is conceivable that some of the included patients carried a genetic defect without clinical expression.

A third shortcoming is that the current medication each patient was regularly taking prior to admission to the ICU was not provided. Knowing the medication of each patient is essential to assess if secondary causes of a NMD were truly excluded.

A fourth shortcoming is that myasthenia was not completely excluded. Though repetitive nerve stimulation was normal in all 12 included patients, acetylcholine receptor antibodies or anti-MUSK antibodies have not been determined. Furthermore, single-fiber electromyography (SF-EMG) to exclude an increased jitter or an increased number of blockings has not been carried out. Excluding myasthenia is crucial as SARS-CoV-2 may not only worsen pre-existing myasthenia but may also trigger the development of myasthenia (Restivo et al., 2020).

There is also no mentioning if myasthenic syndrome was excluded by high-frequency repetitive nerve stimulation. Excluding myasthenic syndrome is crucial as a single patient with chloroquine induced myasthenic syndrome has been recently reported (Koc et al., 2020). Since 11 of the 12 included patients received hydro-chloroquine according to table 1, it is essential to exclude chloroquine-induced myasthenic syndrome in all these patients.

A fifth shortcoming is that Guillain–Barré syndrome (GBS) was not excluded. GBS is increasingly recognized as a complication of COVID-19 and currently as per November 2020 > 100 cases with SARS-CoV-2 associated GBS have been reported (Finsterer, submitted). Excluding GBS is essential as it may go undetected in sedated patients on the ICU. The study did not look for affection of the proximal portions of the peripheral nervous system (PNS). Additionally, no investigations of the cerebrospinal fluid (CSF) have been carried out. Since mononeuropathies of the oculomotor, trochlear, abducens, facial, and glossopharyngeal nerves have been reported, we need to know if function of cranial nerves was intact. Knowing cranial nerve function is crucial with regard to the finding that COVID-19 patients with Miller-Fisher syndrome (MFS) have been reported (Senel et al., 2020).

A six shortcoming is that central nervous system (CNS) causes of respiratory insufficiency have not been acknowledged. There are patients with COVID-19 in whom the disease is complicated by viral or immune encephalitis, ischemic stroke, sinus venous thrombosis, intracerebral bleeding, acute disseminated encephalomyelitis (ADEM), acute, necrotizing encephalopathy, myelitis, or Bickerstaff encephalitis. Cerebral imaging with contrast medium is thus crucial to exclude a central cause of respiratory failure.

Since the outbreak of the epidemic it is known that the infection may go along with myositis. We should know if any of the 12 included patients experienced clinical or electrophysiological manifestations of myositis prior to deterioration of the infection and transfer to the ICU. Did any of them complain about myalgias prior to transfer to the ICU. Recently, several cases with COVID-19 associated dermatomyositis have been reported (Cao et al., 2020). We should know if anti-Ro52 antibodies were positive in any of the included patients.

Since 11 of the included patients received steroids (Cabañes-Martínez et al., 2020), it is necessary to exclude a contribution of steroid myopathy to muscle weakness or respiratory failure. Four patients received meropenem, which may cause hypokalemia and thus may contribute to muscle weakness. From linezolid it is known that it can trigger rhabdomyolysis. The odds ratio for piperacillin/tazobactam to trigger rhabdomyolysis is 2.61. Five of the included patients received this combination. The odds ratio for developing rhabdomyolysis under daptomycin is even 17.94 but patient-5 received it. Azithromycin, frequently given for COVID-19 patients has an odds ratio of 2.94 and it was given to seven in the investigated cohort.

Concerning the exclusion of rhabdomyolysis, we should know peak serum creatine-kinase values, serum and urine myoglobin levels and renal function parameters.

Overall, the interesting report by Cabañes-Martínez et al. (2020) has a number of shortcomings in addition to those listed as limitations in the article, which need to be addressed before

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drawing final conclusions. Work-up for muscle weakness should not only include NCSs of distal nerve segments and needle EMG but also NCSs of proximal nerve segments and SF-EMG. Work-up for respiratory failure has to be more comprehensive than reported and needs to include imaging of the brain and CSF investigations. Myotoxicity of several antibiotics should be considered.

Ethics

Informed consent was obtained. The study was approved by the institutional review board.

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Author contribution

JF: design, literature search, discussion, first draft, critical comments.

Declaration of Competing Interest

There are no conflicts of interest.

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