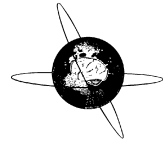




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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.



## Letter to the Editor

### Digging deeper on the neurophysiological assessment in COVID-19 patients



We read with interest the paper entitled “Electrodiagnostic findings in COVID-19 patients: a single centre experience”, by Hameed and Colleagues, recently published in this Journal, presenting a case series of neurological complications in COVID-19 patients (Hameed et al., 2021). Even in the era of a global vaccination campaign, this topic still remains a challenge for clinicians. As the pandemics emerged at a global scale, many neurological manifestations have been increasingly reported worldwide, involving both the Peripheral (PNS) and the Central Nervous System (CNS) (Priori et al., 2020). A recent work also classified the causal relationship between SARS-CoV-2 infection and neurological complications as possible, probable or definite, basing on clinical, laboratory and neuroradiological findings (Ellul et al., 2020). Moreover, a growing body of evidence has strengthened the hypothesis of a neurogenic component underlying the respiratory failure in severe COVID-19 patients (Bocci et al., 2021a; Matschke et al., 2020).

Although the paper by Hameed describes a large cohort of COVID-19 patients, along with a point-to-point correlation between neurophysiological and clinical/laboratory findings, we would like to raise some concerns about the clinical and neurophysiological data as described in this work. In particular, a higher percentage of myopathies (CIM) were described compared to Critical Illness Neuropathy (CIP), while the existing literature reports opposite findings (Bax et al., 2021; Bocci et al., 2021b; Frithiof et al., 2021). Also creatin-phospho-kinase levels seem to suggest a neuropathic rather than a myopathic disorder and the time interval between the hospitalization and the electrodiagnostic (EDX) assessment appears too long for establishing a final diagnosis between these conditions. More important, from a neurophysiological perspective, second-level electrophysiological tests were not included; in particular, the Direct Muscle Stimulation technique is now considered the most reliable and accurate approach to differentiate CIP from CIM (Lefaucheur et al., 2006). All papers describing CIP or CIM in COVID-19 have used non-conventional EDX approaches, even in some pioneering studies reporting a slight predominance of myopathic rather than neuropathic changes (Bagnato et al., 2020). The possibility of a predominant neuropathic involvement is further supported by the recent histopathological demonstration of a “viral trafficking” between the brainstem and lungs, along the vagus nerve (Bulfamante et al., 2021).

This point is of key importance because CIP/CIM differently impact on the recovery and rehabilitation strategies, possibly delaying the discharge from Intensive Care Units.

Finally, regarding non-length dependent neuropathies, the authors reported two confirmed cases of axonal Guillain-Barré Syndrome (GBS), including one patient with Acute Motor Axonal Neuropathy and one with Acute Motor Sensory Axonal Neuropathy. To date, demyelinating GBS (Acute Inflammatory Demyelinating Polyneuropathy) is considered more common than axonal variants in COVID-19 patients (Filosto et al., 2021). GBS following SARS-CoV-2 infection usually shares same clinical and electrodiagnostic findings with non-COVID-19 related polyradiculoneuropathies, despite a very short delay from the primary infection, with neurological signs just emerging few days after respiratory symptoms. Also in these cases, a non-conventional EDX approach may be helpful including, for instance, the evaluation of sensory sparing patterns, as described in axonal as well as in demyelinating forms of GBS (Umapathi et al., 2015).

Overall, it is conceivable that clinical and neurophysiological findings reported by Hameed and co-workers may ultimately be explained by different SARS-CoV-2 variants in Pakistan and Middle East compared to European and American countries. Viral variants may differently affect the Central and the Peripheral Nervous System, thus resulting in different neurological phenotypes.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### References

- Bagnato S, Boccagni C, Marino G, Prestandrea C, D'Agostino T, Rubino F. Critical illness myopathy after COVID-19. *Int J Infect Dis* 2020;99:276–8.
- Bax F, Lettieri C, Marini A, Pellitteri G, Surcinelli A, Valente M, et al. Clinical and neurophysiological characterization of muscular weakness in severe COVID-19. *Neurol Sci*. 2021;42(6):2173–8.
- Bocci T, Bulfamante G, Campiglio L, Coppola S, Falleni M, Chiumello D, et al. Brainstem clinical and neurophysiological involvement in COVID-19. *J Neurol* 2021;268(10):3598–600.
- Bocci T, Campiglio L, Zardoni M, Botta S, Coppola S, Groppo E, et al. Critical illness neuropathy in severe COVID-19: a case series. *Neurol Sci* 2021;3:1–6. <https://doi.org/10.1007/s10072-021-05471-0>
- Bulfamante G, Bocci T, Falleni M, Campiglio L, Coppola S, Tosi D, et al. Brainstem neuropathology in two cases of COVID-19: SARS-CoV-2 trafficking between brain and lung. *J Neurol* 2021;268(12):4486–91. <https://doi.org/10.1007/s00415-021-10604-8>
- Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020;19(9):767–83.
- Filosto M, Cotti Piccinelli S, Gazzina S, Foresti C, Frigeni B, Servalli MC, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. *J Neurol Neurosurg Psychiatry* 2021;92:751–6.
- Frithiof R, Rostami E, Kumlien E, Virhammar J, Fällmar D, Hultström M, et al. Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: A prospective study. *Clin Neurophysiol* 2021;132(7):1733–40.
- Hameed S, Khan AF, Khan S. Electrodiagnostic findings in COVID-19 patients: a single center experience. *Clin Neurophysiol* 2021;132(12):3019–24.

- Lefaucheur JP, Nordine T, Rodriguez P, Brochard L. Origin of ICU acquired paresis determined by direct muscle stimulation. *J Neurol Neurosurg Psychiatry* 2006;77:500–6.
- Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol* 2020;19(11):919–29.
- Priori A, Baisi A, Banderali G, Biglioli F, Bulfamante G, Canevini MP, et al. The many faces of COVID-19 at a glance: A university hospital multidisciplinary account from Milan, Italy. *Front Public Health* 2020;8. <https://doi.org/10.3389/fpubh.2020.575029>.
- Umapathi T, Li Z, Verma K, Yuki N. Sural-sparing is seen in axonal as well as demyelinating forms of Guillain-Barre syndrome. *Clin Neurophysiol* 2015;126:2376–80.

Tommaso Bocci \*

*Clinical Neurology Unit, ASST Santi Paolo & Carlo and Department of Health Sciences, University of Milan, Milan, Italy  
“Aldo Ravelli” Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Milan, Italy*

\* Corresponding author at: “Aldo Ravelli” Center for Neurotechnology and Experimental Brain Therapeutics, Department of Health

Sciences, University of Milan, Via Antonio di Rudinì 8, 20100 Milano, Italy.

E-mail address: [tommaso.bocci@unimi.it](mailto:tommaso.bocci@unimi.it)

Francesco Gentile  
*Clinical Neurology Unit, ASST Santi Paolo & Carlo and Department of Health Sciences, University of Milan, Milan, Italy*

Alberto Priori  
*Clinical Neurology Unit, ASST Santi Paolo & Carlo and Department of Health Sciences, University of Milan, Milan, Italy  
“Aldo Ravelli” Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Milan, Italy*

Accepted 28 October 2021

Available online 27 November 2021