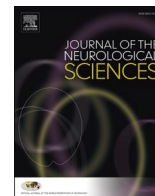




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## COVID-19 and fatigue: Where do we go from here? Response to Ortelli et al.

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#### Dear Editor,

Ortelli et al. [6] presented an intriguing study regarding the neuropsychological and neurophysiological characteristics of post-COVID-19 fatigue. As members of the curation team for 'The Neurology and Neuropsychiatry of COVID-19' blog [2] we have a privileged broad overview of emerging research into the neuropsychiatric sequelae of SARS-CoV-2 infection. In the blog we aim to scrutinise and contextualise findings with regards to the global literature.

The patients included by Ortelli et al. had each suffered profound neurological complications of SARS-CoV-2 infection such as stroke, encephalopathy, critical illness neuropathy / myopathy or Guillain-Barre syndrome. These neurological complications are relatively rare, but more likely to occur in the most severe cases of COVID-19 [1]. As alluded to by the authors, the 12 included patients were thus at the 'severe' end of the COVID-19 disease-spectrum, with likely extended hospital stays and more intensive treatments than the average COVID-19 patient. On discharge, all participants were admitted to a neuro-rehabilitation ward for fatigue, but their length of initial acute hospital stay and level of intervention e.g. intubation and mechanical ventilation, is not detailed. Information relating to the acute phase of illness would therefore help contextualise longer-term studies of this kind, including the generalisability of findings to the wider population. Furthermore, COVID-19 cases without such severe neurological complications but with ongoing fatigue, both in those hospitalised with severe initial COVID-19 and without, would be important groups to study with the same methodologies.

It is possible that the fatigue comprehensively demonstrated in this study could at least in part be attributed to protracted hospitalisation [5]. Taboada et al. [8] identified length of hospitalisation as a predictor of greater impairment in functional fatigue status; highlighting further the relevance of reporting functional outcomes in fatigue research. Fatigue aside, prolonged hospitalisation may be linked to other neuropsychiatric complications following acute COVID-19 infection. For example, length of ICU stay has been significantly correlated with severe encephalopathy [5].

Considering this, and whilst a control group of healthy individuals allows for rigorous comparisons to be made, it may be appropriate in future for controls, as suggested by the authors, to instead reflect the effects of prolonged hospitalisation on fatigue and other outcomes. We

envisage COVID-19 patients compared against a control group of patients hospitalised for conditions other than COVID-19 and matched not only for age and sex, but length of hospitalisation. Other authors compared post-SARS patients with matched fibromyalgia patients [4]. This approach may be relevant in light of the growing body of research drawing parallels between post-COVID neuropsychiatric illness and conditions also typified by fatigue, such as fibromyalgia and chronic fatigue syndrome (CFS) [3].

Ortelli et al. conducted a comprehensive battery of neuropsychiatric and neurophysiological testing. In addition to impairment measured by outcomes of this sort, it will be valuable in future to measure disability in terms of real-world outcomes. For example, the practical implications of reduced functional ability due to persistent fatigue following SARS-CoV-2 infection may manifest as significantly lower rates of employment at 8–12 weeks following acute infection [9]. The inclusion of functional outcome data would significantly enhance the contextual implications of mechanistic data in future studies.

Epidemiological studies and meta-analyses continue to be published which estimate the prevalence and persistence of symptoms such as fatigue in COVID-19 patients, both hospitalised and non-hospitalised [7]. We anticipate that further studies in larger samples, which describe a range of COVID-19 severity, include disease controls, and report functional outcomes, will improve our understanding of how SARS-CoV-2 causes persistent fatigue in a significant proportion of survivors to hopefully improve treatment of this often highly disabling and potentially chronic symptom.

#### Declaration of Competing Interest

Nothing to declare.

#### References

- [1] M. Abenza-Abildúa, M. Ramírez-Prieto, R. Moreno-Zabaleta, N. Arenas-Valls, M. Salvador-Maya, C. Algarra-Lucas, B. Rojo Moreno-Arrones, B. Sánchez-Cordón, J. Ojeda-Ruiz de Luna, C. Jimeno-Montero, F.J. Navacerrada-Barrero, C. Borrue-Fernández, E. Malmierca-Corral, P. Rufz-Secod, P. González-Ruanod, I. Palmí-Cortés, J. Fernández-Travieso, M. Mata-Álvarez de Santullano, M.L. Almarcha-Menargues, G. Gutierrez-Gutierrez, J.A. Palacios Castaño, R. Alonso Esteban, R. Gonzalo-García, C. Pérez-López, Neurological complications in critical patients

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- with COVID-19, *Neurologia (English Edition)* 35 (9) (2020) 621–627, <https://doi.org/10.1016/j.nrleng.2020.07.012>.
- [2] M. Butler, C. Watson, A. Rooney, J. Song, J. Badenoch, S. Pick, B. Cross, D. Hafeez, M. Lim, H. Morrin, E. Rengasamy, L. Thomas, S. Ralovska, R. Sundaram, S. Ray, V. Singh, I. Conti, S. Pandey, S. Chakraborty, Z. Hussain, E. Burchill, E. Aniwattanapong, D. Walton, J. Rogers, I. Koychev, M. Ellul, T. Solomon, T. Pollak, B. Michael, T. Nicholson, The Neurology and Neuropsychiatry of COVID-19 | JNNP blog, 2020 [online] JNNP blog. Available at: <https://blogs.bmj.com/jnnp/2020/05/01/the-neurology-and-neuropsychiatry-of-covid-19/>. (Accessed 4 March 2021).
- [3] A. Komaroff, L. Bateman, Will COVID-19 Lead to Myalgic encephalomyelitis/chronic fatigue syndrome? *Front. in Med.* 7 (2021) 1132, <https://doi.org/10.3389/fmed.2020.606824>.
- [4] H. Moldofsky, J. Patcai, Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study, *BMC Neurol.* 11 (1) (2011) 37, <https://doi.org/10.1186/1471-2377-11-37>.
- [5] V. Nersesjan, M. Amiri, A. Lebech, C. Roed, H. Mens, L. Russell, L. Fonsmark, M. Berntsen, S. Sigurdsson, J. Carlsen, A. Langkilde, P. Martens, E. Lund, K. Hansen, B. Jespersen, M. Folke, P. Meden, A. Hejl, C. Wamberg, M. Benros, D. Kondziella, Central and peripheral nervous system complications of COVID-19: a prospective tertiary center cohort with 3-month follow-up, *J. Neurol.* 13 (2021) 1–19, <https://doi.org/10.1007/s00415-020-10380-x>.
- [6] P. Ortelli, D. Ferrazzoli, L. Sebastianelli, M. Engl, R. Romanello, R. Nardone, I. Bonini, G. Koch, L. Saltuari, A. Quartarone, A. Oliviero, M. Kofler, V. Versace, Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: insights into a challenging symptom, *J. Neurol. Sci.* 420 (2021) 117271, <https://doi.org/10.1016/j.jns.2020.117271>.
- [7] J. Rogers, C. Watson, J. Badenoch, B. Cross, M. Butler, J. Song, D. Hafeez, H. Morrin, E. Rengasamy, L. Thomas, S. Ralovska, A. Smakowski, R. Sundaram, C. Hunt, M. Lim, D. Aniwattanapong, V. Singh, Z. Hussain, S. Chakraborty, E. Burchill, K. Jansen, H. Holling, D. Walton, T. Pollak, M. Ellul, I. Koychev, T. Solomon, B. Michael, T. Nicholson, A. Rooney, The neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives, *Medrxiv* (2021), <https://doi.org/10.1101/2021.02.24.21252335> in press.
- [8] M. Taboada, A. Carriena, E. Moreno, N. Rodríguez, M. Domínguez, A. Casal, V. Riveiro, M. Diaz-Vieito, L. Valdés, J. Álvarez, T. Seoane-Pillado, Post-COVID-19 functional status six-months after hospitalization, *J. Inf.* 14 (2020) 45, <https://doi.org/10.1016/j.jinf.2020.12.022>.
- [9] L. Townsend, A. Dyer, K. Jones, J. Dunne, A. Mooney, F. Gaffney, L. O'Connor, D. Leavy, K. O'Brien, J. Dowds, J. Sugrue, D. Hopkins, I. Martin-Loeches, C. Ni Cheallaigh, P. Nadarajan, A. McLaughlin, N. Bourke, C. Bergin, C. O'Farrelly, C. Bannan, N. Conlon, Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection, *PLoS One* 15 (11) (2020), <https://doi.org/10.1371/journal.pone.0240784> p.e0240784.

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