



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.



Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

The authors' response: A diagnostic confusion between serotonin syndrome and neuroleptic malignant syndrome

Dear Editor,

Thank you for the comments on our article. First, we could not describe the details of symptoms or the differential diagnosis in the text because of the word limit; therefore, we sincerely appreciate the authors/editors providing us the opportunity to describe the details of neuroleptic malignant syndrome (NMS) in patients with COVID-19 infection.

The authors proposed a possible diagnosis of serotonin syndrome (SS) in our reported two cases of NMS following COVID-19 infection because both cases fulfilled the Sternbach's criteria of SS [1]. However, several aspects must be addressed to differentiate NMS from SS in these cases. First, although SS is characterized by neuromuscular hyperreactivity (tremor, hyperreflexia, and myoclonus), these physical findings were not detected in the two cases. Second, remarkably elevated creatine kinase levels were observed. Third, the authors described that rapid onset and rapid resolution of fever pattern were more likely in SS, rather than in NMS; however, the high-grade fever (>39 °C) persisted for approximately five days in case 1 and three days in case 2. Fourth, another case of NMS in a patient with COVID-19 infection has been recently published [2].

In case 1, hyperreactivity symptoms such as tremor and myoclonus were not observed. Furthermore, although there was no rigidity of the major joints, rigidity of the fingers on both sides was recognized. In addition, there was no history of use of selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors. This patient had loose stools and watery stools since the time of admission, but no apparent improvement was observed even after the discontinuation of the causative drugs.

In case 2, hyperreactivity and rigidity findings such as tremor and myoclonus were not recognized. Although not pursued in the submitted paper, we started suvorexant (orexin receptor antagonist) on day 5 at the same time as risperidone for treating delirium. Later, risperidone was discontinued on day 8 owing to the suspicion of NMS, but suvorexant was not considered to be the causative drug and continued without discontinuation until day 20. Despite continuing suvorexant, as there was improvement in the symptoms, this drug cannot be considered as a causative agent. This patient had loose stools and mud stools since the time of admission, but no improvement was found even after the discontinuation of suvorexant.

Although no typical symptoms of SS were observed, a possibility of coexistence of both NMS and SS exists, as the authors proposed. Therefore, as we have proposed in the manuscript, careful consideration of the development of NMS is necessary in the management of patients with COVID-19 infection [3].

Funding

None.

References

- [1] Sternbach H. The serotonin syndrome. *Am J Psychiatry*. 1991;148:705–13.
- [2] Kajani R, Apramian A, Vega A, Ubhayakar N, Xu P, Liu A. Neuroleptic malignant syndrome in a COVID-19 patient. *Brain Behav Immun*. 2020;18 S0889–1591(20)30838–2.
- [3] Soh M, Hifumi T, Isokawa S, Shimizu M, Otani N, Ishimatsu S. Neuroleptic malignant syndrome in patients with COVID-19. *Am J Emerg Med*. 2020;22 S0735–6757(20)30384–3.

Mitsuhito Soh MD

Emergency and Critical Care Medicine, St. Luke's International Hospital, Tokyo, Japan

Toru Hifumi MD, PhD

Emergency and Critical Care Medicine, St. Luke's International Hospital, Tokyo, Japan

E-mail address: hifumitoru@gmail.com

Shutaro Isokawa MD

Emergency and Critical Care Medicine, St. Luke's International Hospital, Tokyo, Japan

Masato Shimizu MD

Emergency and Critical Care Medicine, St. Luke's International Hospital, Tokyo, Japan

Norio Otani MD

Emergency and Critical Care Medicine, St. Luke's International Hospital, Tokyo, Japan

Shinichi Ishimatsu MD, PhD

Emergency and Critical Care Medicine, St. Luke's International Hospital, Tokyo, Japan

16 June 2020

Available online xxxxx