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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A diagnostic confusion between Serotonin syndrome and Neuroleptic malignant syndrome

Dear Sir

Soh et al. reported Neuroleptic malignant syndrome (NMS), fulfilling the Levenson's criteria, in two patients with COVID-19 [1]. The clinical phenomenon of NMS and Serotonin syndrome (SS) is very similar, and differentiation between these two clinical disease entities may be difficult, as patients can meet the criteria for both syndromes [2]. The two main points which help in differentiating SS with NMS are (i) type of precipitating drugs (serotonergic drug vs neuroleptic drug) and (ii) presence of neuromuscular hyperactivities (clonus and hyperreflexia vs hyporeflexia) [2,3]. Although the authors failed to report the presence or absence of clonus and hyperreflexia, the reported clinical features in both patients fit in the frame of typical SS. In fact, both cases fulfilled the Sternbach's criteria of SS [4]. Unfortunately, the authors did not discuss the differential diagnosis in both cases.

The authors' claim that midazolam and fentanyl triggered NMS in case-1 is far from reality. According to the description of case-1, most of the symptoms (fever, altered consciousness, and diaphoresis) appeared after the discontinuation of midazolam. So, a temporal association between midazolam initiation and the development of clinical features suggestive of NMS is missing here. To the best of our literature search, I did not find even a single case of SS precipitating by midazolam. The one citation provided by the authors in this regard is not available in the public domain. Similarly, the authors did not provide even a single citation where fentanyl has precipitated NMS. In fact, just contrary to authors' claims, benzodiazepines (including midazolam) and fentanyl are used as supportive measures in patients with MNS [5].

Both patients received a combination of fentanyl, propofol, and favipiravir. Fentanyl has serotonergic properties, and is known to trigger SS [6]. Propofol has, also, been shown to precipitate SS in a few cases [7]. DeSilvaa et al. have reported 5 patients of SS in HIV patients, triggered by ritonavir [8]. Recently, Serrano et al. have noted SS in COVID patients, triggered by a fixed combination of lopinavir/ritonavir [9]. Therefore, a possibility of SS even by favipiravir can be speculated. Case 2 had also received risperidone, an atypical neuroleptic. So, a possibility of NMS cannot be ruled out in case 2. However, a possibility of SS is more likely, as the patient had been on three drugs (fentanyl, propofol, and favipiravir) that may precipitate SS. Moreover, risperidone may elevate 5-HT and may trigger SS. There are several case reports of SS induced by risperidone [10]. However, a patient can have NMS and SS simultaneously if they receive a combination of neuroleptic and serotonergic agents. So, a possibility of coexistence of both NMS and SS also exists here.

There are a few other features that may help in differentiating SS with NMS. The pattern of onset and evolution of symptoms may be a diagnostic clue in some patients. While patients with SS have a rapid onset and rapid progression of symptoms, NMS typically evolves slowly. Similarly, while SS generally resolves within a few days after discontinuing the causative drugs and initiation of therapies, NMS usually takes more than 10–20 days to remit [2,3]. Figs. 1 and 2 [1] demonstrate rapid onset and rapid resolution of fever, a pattern more likely in SS, rather NMS.

Serotonin syndrome typically results from an increase in the intrasynaptic concentration of serotonin (5-HT), especially in the brainstem. However, approximately 90% of the total serotonin in the body is stored in the enterochromaffin system of the gastrointestinal tract and it helps in gastrointestinal motility. So, gastrointestinal features, such as diarrhea, nausea, vomiting, increased bowel sounds are common in SS, whereas these findings are usually not observed with NMS [2]. However, the authors did not mention whether these symptoms were absent or present.

Both patients had very high creatine kinase (CK) levels. A very high CK level is more characteristic of NMS. However, there are several case reports of SS with a very high CK level [11]. A diagnosis of NMS cannot be made just on the basis of high CK levels. Moreover, COVID patients may have associated myositis with very high CK levels [12]. So, COVID may be a contributing factor for very high CK levels in both patients.

The management for mild or moderate cases of SS and NMS is almost similar; discontinuation of precipitating agents and supportive measures. However, severe cases need specific therapy; dantrolene for NMS and cyproheptadine in SS. Both patients had altered behavior, very high temperature, and markedly elevated CK levels. Why these patients were not treated with dantrolene or similar drugs if the working diagnosis was NMS. It could have been a diagnostic clue in both patients.

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Declaration of competing interest

None to declare.

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