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## Delirium in hospitalized COVID-19 patients: A case series

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Dear editor,

Since the 30th January 2020, when the World Health Organization (WHO) declared COVID-19 a public health emergency (Sohrabi et al., 2020), multiple cases of patients who developed neuropsychiatric symptoms associated with the infection have been described. One of the main difficulties to characterize these symptoms is the heterogeneity in terms of their presentation and the atypical evolution of the disease (Pezzini and Padovani, 2020; Li et al., 2020a). It is estimated that between 28–38% of patients admitted for SARS-COV-2 infection, especially those with severe symptoms, will develop a condition compatible with delirium (Ezpeleta, 2020; Ahmad and Rathore, 2020).

In addition to the already known precipitating factors (Rieck et al., 2020; Gómez and Camba, 2017; O'Hanlon and Inouye, 2020; Hsieh et al., 2020), other factors within the specific framework of COVID-19 are described: direct impairment to the central nervous system, induction of inflammatory mediators, multi-organ failure, sedation, prolonged mechanical ventilation, immobilization, and environmental factors (quarantine, isolation, health situation) (Kotfis et al., 2020; Talevi et al., 2020; Torales et al., 2020; Rodriguez-Jimenez et al., 2021).

The categorization of a particular delirium phenotype associated with SARS-COV-2 infection has not been considered to date, although it is already beginning to be postulated (Wilson et al., 2020; Hawkins et al., 2020; Palomar-Ciria et al., 2020). A specific electroencephalographic (EEG) pattern of COVID encephalopathy has been described, differentiated from other hypoxic situations (Pastor et al., 2020a), and that could explain certain clinical particularities that we will describe.

We describe a series of clinical cases assessed by the Hospital de la Princesa's Liaison Psychiatry Team of patients admitted for severe SARS-COV-2 infection between April and September 2020 who presented with clinical symptoms compatible with delirium and which stood out for their atypicality both in their phenomenology and in their onset and clinical evolution.

Most of the cases (4) had been admitted into the Intensive Care Unit (ICU), but in all of them the assessment was carried out in the internal medicine or pulmonology hospitalization unit within the first 24 h after the request for clinical input. The assessment and follow-up reviews were carried out by the members of the Liaison Psychiatry Team, specifically a consultant psychiatrist and a third year psychiatry trainee doctor. Daily follow up reviews were carried out until resolution of the described episodes.

During the previously mentioned months, a total of 6 patients admitted for SARS-COV-2 infection presented with delirium symptoms with the previously mentioned particularities. The cases are described below.

### 1. Case 1 (Pastor et al., 2020b)

A 63-year-old gentleman, an active physician, with no previous mental health history, who was admitted into the intensive care unit (ICU) for SARS-COV-2 infection. After achieving respiratory stability, and already in the hospitalization unit, he began to present with symptoms of atypical delirium. He was assessed on the 19th day of admission, where confabulations, a significant impairment of verbal and semantic fluency (psychometrically measured) and a reasonable level of attention stood out. On a behavioral level, at night, he began with a striking occupational delusion, in his case giving orders for treatment. High doses of antipsychotics were used (initially aripiprazole and quetiapine, and once vascular etiology was ruled out, risperidone up to 6 mg per day). The complementary tests that were carried out were normal, except for the electroencephalogram (EEG) which was reported with the following conclusions: "mild encephalopathy and left temporal irritative activity". The episode lasted 9 days, with a sudden and complete resolution. One month after his admission, the patient's cognitive impairment was resolved and allowed him to resume his working activities.

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## 2. Case 2

A 61-year-old lady with no previous psychiatric history and without any previous functioning concerns who was admitted for SARS-COV-2 infection requiring admission to the ICU. On the 18th day of admission, after a few days in the unit, with respiratory stability, she presented with symptoms of hypervigilance, difficulties in telling a story in order, auditory hallucinations, and a disorganized speech that at times expressed anguish and where delusional ideas were elicited. The normal attention span that she presented with drew our attention, as it also did the absence of behavioral repercussions. She was prescribed risperidone 6 mg per day, which resulted in a sudden improvement 72 h after the start of treatment. Throughout the hospitalization, the patient did not present side effects related to the antipsychotic treatment. At the time of her discharge, no drugs were prescribed, no cognitive sequelae had arisen, with the patient presenting with a *restitutio ad integrum*.

## 3. Case 3

A 65-year-old gentleman with no previous psychiatric history, an active engineer, who required prolonged hospitalization for SARS-COV-2 infection and ICU care. The onset of symptoms occurred after respiratory stability was achieved on day 23rd of admission and consisted of disorientation, irritable mood, and hostility, as well as disorganized speech where poorly structured delusional ideas and false recognitions were elicited. There were no clear attention deficits or behavioral changes. Due to the referred symptoms, treatment with Risperidone 4 mg per day was initiated, which had to be subsequently increased to 6 mg per day due to a lack of sufficient response. Similar to the rest of the cases in this series, there was a sudden improvement in his condition, in this case six days after the onset, being the patient able to regain insight into his symptoms. Side effects due to antipsychotics were not described. At discharge, no cognitive sequelae were elicited, although, in contrast to the other cases, anxiety and depressive symptoms were observed in relation to the experienced situation. Therefore, Mirtazapine 15 mg nocte was started, which was later stopped after the second follow-up appointment. The diagnosis at outpatient discharge was an adjustment disorder.

## 4. Case 4

A 76-year-old lady with no previous mental health history and no previous functioning concerns, who required prolonged admission for SARS-COV-2 infection. The onset occurred on day 59th of her admission after respiratory stability was achieved and consisted of disorientation, verbiage, and disinhibition, as well as a slightly disorganized speech where poorly structured delusional ideas and sensory-perceptual abnormalities were elicited in the form of visual hallucinations. The presence of a good level of attention and the absence of behavioral changes or emotional repercussions stood out. As a result, it was necessary to start treatment with Risperidone 6 mg per day and Gabapentin 900 mg per day with a sudden recovery, although not sudden compared to the other cases. At her discharge, there were no cognitive sequelae, although she did present with reactive anxiety, so treatment with Gabapentin every 12 h was maintained.

## 5. Case 5

A 51-year-old woman with no previous mental health history, an active worker, who required admission for SARS-COV-2 infection. The onset of symptoms was described after respiratory stability was achieved during the first day of hospitalization and consisted of a fluctuating polymorphous framework where disorientation, sensorial-perceptual abnormalities in the form of visual hallucinations, and the presence of disorganized speech with dreamlike content without clear affective repercussions were elicited. As in previous cases, the normal attention

span and the absence of behavioral changes were notable. Given the above-described, treatment with Risperidone 2 mg per day was initiated, after which the patient presented a sudden recovery after 4 days and an increase in dose to 4 mg per day. During her entire stay, no side effects related to antipsychotic treatment were observed. On the last day of her admission, there were no cognitive sequelae, hence the patient presented with a *restitutio ad integrum* without the need for treatment at her discharge.

## 6. Case 6

A 62-year-old lady with no previous mental health history, an active domestic worker, who required prolonged admission for SARS-COV-2 infection and ICU care. The onset of the condition developed after respiratory stability was achieved in the conventional hospitalization unit on day 40th of admission and consisted of disorientation to place, verbiage, as well as disorganized speech where delusional ideas of harm, delusional interpretations and irrevocable convictions of being in her native country were elicited. As a noteworthy peculiarity, the good level of attention and the absence of repercussion on an emotional and behavioral level stood out. Given the above mentioned, treatment with Risperidone 3 mg per day was initiated, and the patient presented a clear and sudden improvement after 4 days. On the last day of her admission, there were no cognitive sequelae, with the patient presenting with *restitutio ad integrum*. Nonetheless, due to the velocity of her recovery it was not possible to carry out an adequate down titration of the antipsychotic, so the patient was prescribed 1 mg of Risperidone per day at discharge, which was stopped in the first outpatient appointment.

In accordance with what is described in these case series, we highlight the following particularities:

The symptoms emerge at a time of respiratory stability. The onset of the symptoms is striking considering the stress diathesis model, since all the described cases are patients without prior risk factors and the condition develops at a time of the hospitalization when the clinical severity of SARS-COV-2 infection had remitted and without the patient having previously presented with symptoms compatible with delirium (Mattison, 2020; Emmerton and Abdelhafiz, 2020). As we have mentioned, none of the patients had a history of mental health or had cognitive vulnerability.

In none of the cases could a temporal pattern be established between certain drugs used for the treatment of SARS-CoV2 infection (hydroxychloroquine, lopinavir/ritonavir or corticosteroids) and that were considered as possible contributors (Bogaczewicz and Sobów, 2017; Sato et al., 2020; Anmella et al., 2020). In fact, half of the reported cases occurred when hydroxychloroquine and lopinavir/ritonavir were no longer being used as treatments.

The phenomenological atypicality of delirium, with little or no attentional deterioration compared to a severe impairment in memory and language with significant behavioral repercussions (Hübscher and Isenmann, 2016; Gupta et al., 2008; Meagher and Trzepacz, 1998).

A sudden improvement in all the cases, with incongruity between the memory of what was experienced and the behavioral repercussion, and without sustained cognitive impairment, does not compare to what is commonly described in delirium, which is related to cognitive deterioration at discharge (Goldberg et al., 2020).

High doses of antipsychotics were used, going against the clinical practice guidelines advice (Nikooie et al., 2019) and without the empirical presence of notable side effects.

Although the absence of structural damages, including those of vascular etiology, was ruled out with neuroimaging in all cases (computed tomography scan), performing a lumbar puncture was not possible in any of the cases. The EEG was performed only in the first one and its result was presented as paradigmatic of this described characteristic electroencephalographic pattern (Pastor et al., 2020a). Due to the global pandemic framework and the healthcare national system needs by that moment, it was not always possible to perform tests aimed

at a finer etiopathological parentage, such as, an EEG or a lumbar puncture. In fact, in case 1, a relationship between the EEG result and clinical atypicality is hypothesized, supported by this other series of cases (Pastor et al., 2020a, 2020b).

The proposed hypothesis gives fundamental importance to the possible neurotropism presented by COVID-19 (Iadecola et al., 2020; Costello and Dalakas, 2020; Li et al., 2020b; Yachou et al., 2020). In addition to symptoms of delirium, other clinical syndromes are beginning to be directly related to the infection, among which stand out psychotic symptoms not associated with delirium (Parra et al., 2020; Rentero et al., 2020), encephalitis and cerebral infarction (Koralnik and Tyler, 2020; Garg, 2020), which are ruled out in the presented cases. Knowing the clinical manifestations of these symptoms is of great importance for proper management and advice. Also, homogeneous descriptions and nomenclatures are not used, which constitutes a limitation in the publications of neuropsychiatric symptoms in patients admitted for SARS-CoV-2 infection.

Given the presence of clinical symptoms compatible with delirium in patients with severe SARS-CoV-2 infection with similar characteristics in terms of their phenomenology, time of onset, and resolution, we consider a direct relationship between the infection, the conditions of hospital admission, the previous psychosocial situation and the appearance of these characteristic symptoms to be probable. More studies will be necessary to confirm this hypothesis.

## Declaration of Competing Interest

No conflict of interest.

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