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## Short communication

## Psychotic symptoms in COVID-19 patients. A retrospective descriptive study

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## ABSTRACT

Psychotic symptoms have been related to other coronavirus infections. We conducted a single-centre retrospective and observational study to describe new-onset psychotic episodes in COVID-19 patients. Ten patients infected by the novel coronavirus with psychotic symptoms and no previous history of psychosis were identified by the emergency and liaison psychiatry departments. Nine of the cases presented with psychotic symptoms at least two weeks after the first somatic manifestations attributed to COVID-19 and receiving pharmacological treatment. Structured delusions mixed with confusional features were the most frequent clinical presentations. Hence, COVID-19 patients can develop psychotic symptoms as a consequence of multiple concurrent factors.

## 1. Introduction

Spain is being one of the most affected countries by the COVID-19 pandemic, with more than 222.857 confirmed cases and 26.251 deaths on the 9th of May (World Health Organization, 2020). To this date, psychiatry research has mainly focused on the emotional impact of the coronavirus pandemic on the general population (Wang et al., 2020) and healthcare workers (Kisely et al., 2020; Spoorthy, 2020). Psychological reactions, such as depression, anxiety, panic attacks and post-traumatic symptoms, have been described (Spoorthy, 2020). Recently, a Spanish research group has reported a small number of psychotic episodes, in non-infected patients, probably triggered by the stressful scenario caused by the pandemic (Valdés-Flrido et al., 2020). However, less attention has been paid to study the possible direct role of the virus (SARS-CoV-2) on the development of neuropsychiatric symptoms, such as secondary psychosis (Troyer et al., 2020).

New-onset psychotic symptoms have been described in patients infected by previous coronaviruses, such as SARS-CoV and MERS-CoV, considering as possible etiological factors viral exposure, treatments used to manage the infection, and psychosocial stress (Brown et al., 2020; Lee et al., 2004; Mrcpsych et al., 2020). Thus, it would not be surprising to see the SARS-CoV-2 following the same trend. In fact, some acute neurological symptoms have already been described in patients affected by the novel coronavirus (García, 2020; Mao et al.,

2020; Mrcpsych et al., 2020), as well as psychotic symptoms in few recent papers (Ferrando et al., 2020; Varatharaj et al., 2020).

As emergency and liaison psychiatrists working at one of the largest teaching hospitals in Madrid, we have observed a growing number of acute psychotic syndromes in patients infected by SARS-CoV-2 and with no previous history of psychosis (Rentero et al., 2020). Therefore, the aim of our study is to gather their main clinical features in order to identify possible risk factors and differences from non-organic psychosis.

## 2. Methods

## 2.1. Study design and participants

We identified all patients over 18 years old assessed by the emergency and liaison psychiatry departments at Hospital 12 de Octubre within the months of March and April 2020. During those months this 1300 bedded tertiary-level teaching hospital reached more than 3000 admissions and 10000 evaluations of patients clinically compatible with COVID-19 disease at the emergency department (Hospital 12 de Octubre, 2020). Only patients with new-onset psychotic symptoms and confirmed diagnosis of SARS-CoV-2 infection (by real-time PCR) were enrolled in this study. In accordance with diagnostic criteria for “Medication-Induced Psychotic Disorders” and “Psychotic Disorders

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Due to Another Medical Condition” (American Psychiatric Association, 2013) we decided to exclude those cases that completely met the diagnostic criteria for delirium. Patients with previous history of severe mental disorders were also excluded.

The study was approved by the Hospital Ethics Committee and patients’ information was handled as stated in Spanish and European regulations on data protection and patients’ digital rights.

## 2.2. Variables

Sociodemographic, clinical, radiological, management and outcome data were retrospectively retrieved from patients’ medical records during the hospitalization period. Within past medical history, cardiovascular risk factors and respiratory diseases were especially investigated because of the associated poorer prognostic outcomes (Chen et al., 2020). Non-psychiatric symptoms were recorded based on previous studies’ descriptions of COVID-19 manifestations (Chen et al., 2020; Mao et al., 2020). Poor prognosis data were also based on analytical, radiological findings, and need of admission to an Intensive Care Unit (ICU), in accordance with previous papers (Han et al., 2020; Mao et al., 2020; Mehta et al., 2020) and the COVID-19 protocol of our hospital. Confusional and psychotic symptoms were systematically retrieved from the items included in the Delirium Rating Scale-Revised-98 (DRS-98, spanish version) (Fonseca et al., 2005) and clinical notes.

## 2.3. Analyses

Descriptive analyses were performed using IBM SPSS software version 20. Results are expressed as means in case of numerical variables, or counts and percentages in case of categorical variables.

## 3. Results

Sixteen patients with COVID-19 and new-onset psychotic symptoms were initially identified. Six of them were diagnosed as delirium and excluded from the study. 60% of the sample were males, and the mean age was of 54.1 years (Standard Deviation: 10,67). Some patients had cardiovascular risk factors such as dyslipidemia (30%), hypertension (20%) and obesity (10%). None of them had respiratory problems nor were immunosuppressed. Main physical symptoms were fever (90%), cough (90%), dyspnea (80%), fatigue (50%), myalgias (40%), diarrhea (30%) and anorexia (20%). One patient suffered multiple thrombotic events (cerebral, pulmonary, and deep venous thrombosis) and other two patients presented pulmonary thromboembolisms.

All patients presented with delusions (50% of them were highly structured), followed by orientation/attention disturbances (60%), auditory and visual hallucinations (40% and 10%, respectively). None of them had family/personal history of drug use or severe mental disorder. Only one patient had not received any treatment before the onset of psychotic symptoms and had not presented other physical symptoms. This case was only attended because of the behavioral disturbances. The other patients had been previously treated with hydroxychloroquine (HCQ) ( $n=9$ ), lopinavir/ritonavir ( $n=6$ ), tocilizumab ( $n=6$ ), corticosteroids ( $n=7$ ) and antibiotics ( $n=9$ ). 50% of the patients had undergone ICU treatment (for a mean of 15,5 days). In 80% of patients psychotic symptoms appeared more than two weeks after the first somatic manifestation attributed to COVID-19 and resolved in less than two weeks.

Delusions of prejudice, persecutory and referential beliefs were the most frequent outcomes. Confusional symptoms were not present in the patient whose psychosis debut was not preceded by COVID-19 treatment. In this particular case, laboratory and radiological results were normal, schizoid premorbid personality traits were described by relatives and he was under important stress because of his parents’ severe COVID-19 disease. Management data and complementary test results of all patients are summarized in Table 1.

**Table 1**

Management data and complementary tests. CRP (C-Reactive Protein); LDH (Lactate Dehydrogenase); CK (Creatine-Kinase); CT (Computed Tomography of the brain); MRI (Magnetic Resonance Imaging of the brain); LP (Lumbar Puncture); EEG (Electroencephalography).

Variable	All patients ( $n = 10$ ) $n^{\circ}$ (%)	
Antipsychotics used during hospitalization $n$ (mean dose)	Olanzapine	7 (15)
	Aripiprazole	1 (10)
	Risperidone	5 (2,2)
	Haloperidol	3 (2)
Antipsychotic treatment at discharge $n$ (mean dose)	No	1 (10%)
	Yes (monotherapy)	9 (90%)
Analytical findings	Olanzapine 4 (8.75) OR Risperidone 5 (1.8)	
	Lymphopenia	8 (80%)
	CRP elevation	6 (60%)
	LDH elevation	9 (90%)
	D-dimer elevation	7 (70%)
	Low platelet count	0
	CK elevation	6 (60%)
Radiological findings	Ferritin elevation	7 (70%)
	Absence of infiltrates	1 (10%)
	Unilateral infiltrates	1 (10%)
	Bilateral infiltrates	8 (80%)
Complementary tests	CT	Not available 2 (20%) Normal 7 (70%) Acute ischemic event 1 (10%)
	MRI	Not available 7 (70%) Normal 1 (10%) Small vessel chronic ischemic disease 1 (10%) Acute ischemic event 1 (10%)
	LP	Not available 6 (60%) Normal 3 (30%) Glycorrhachia and proteinorrachy 1 (10%)
	EEG	Not available 5 (50%) Normal 4 (40%) Abnormal findings 1 (10%)

## 4. Discussion

We report several cases of patients infected by SARS-CoV-2 that experienced new-onset psychosis during the infection. These psychotic symptoms were usually at the forefront and characterized by thoughts of reference and structured delusional beliefs, as the three cases analysed by Ferrando et al. (2020). In contrast to their observations, we found confusional features at the onset of psychiatric manifestations in six patients (disorientation to space and time, and inattention), although these symptoms disappeared quicker that delusional beliefs did. This finding is not surprising if we take into account that 50% of our sample had received ICU-treatment and 80% had bilateral pneumonia, in contrast to the cases of Ferrando et al. (2020) that were physically asymptomatic and had not previously received treatment for COVID-19. Confusional symptoms and agitation in the COVID-19 pandemic have been mainly described in patients admitted to ICU (Kotfis et al., 2020; Mrcpsych et al., 2020) and severe disease (Mao et al., 2020). Our cases experienced a fast recovery with low doses of antipsychotics, as observed in other virus-induced psychosis (Brown et al., 2020) and recent reports in COVID-19 patients (Ferrando et al., 2020).

We have hypothesized that the patient whose psychosis debut was not preceded by COVID-19 treatment/manifestation could be an example of a primary psychotic episode triggered by stress (Beards et al., 2013), with a poorer prognosis because of the premorbid schizoid

personality traits (Castagnini and Galeazzi, 2016). However, the rest would correspond to secondary psychotic episodes because of several reasons: (1) absence of predisposing factors such as family history of severe mental illness or substance abuse; (2) atypical age of debut; (3) subacute onset of psychotic symptoms (less than one week) and fast recovery (maximum 2 weeks) on low antipsychotic doses; and (4) presence of confusion mixed with the typical psychotic symptoms. The pathogenic mechanism underlying the observed psychiatric manifestations remains unclear and could be multifactorial.

One of the theories involves CNS invasion, as it has been described in previous coronavirus infections (Nath, 2020; Troyer et al., 2020; Zhou et al., 2020). Even though the virus has been isolated from samples of cerebrospinal fluid (Wu et al., 2020), Helms et al. (2020) had negative results in the seven samples analysed. Unfortunately, we could not carry out this procedure to elucidate this question.

Another mechanism implies the systemic hyperinflammatory response associated with severe cases of COVID-19 pneumonia (Mehta et al., 2020; Ruan et al., 2020), known as “the storm of cytokines”. In our sample we found elevation of CRP and ferritin in six and seven cases, respectively. The hyperinflammatory response in CNS could explain confusional (Martínez and Velasco, 2020) and psychotic symptoms, since cytokines have been also related to the pathogenesis of primary psychotic disorders (Serrano-Castro et al., 2020). The hypercoagulable state triggered by “the storm of cytokines” could also provoke ischemic events and, thus, play a role in the genesis of neuropsychiatric symptoms. This could be aggravated by prolonged immobilization, use of corticoids, hypoxia and higher presence of cardiovascular risk factors within severe patients (Kumral and Öztürk, 2004; Kunal et al., 2020). According to previous reports (Helms et al., 2020), in our study, one patient suffered an acute ischemic stroke, three subjects had thrombotic events in other territories, and 70% of the sample had D-Dimer elevation.

Iatrogenic factors should also be taken into consideration. Psychotic and confusional symptoms are adverse effects described with the use of corticosteroids and HCQ (Mascolo et al., 2018; Sato et al., 2020; Warrington and Bostwick, 2006). The risk for HCQ is increased with doses greater than 6.5 mg/kg/day (Mascolo et al., 2018) and co-administration of CYP3A4 inhibitors (such as lopinavir/ritonavir) and glucocorticoids (Mascolo et al., 2018). No psychiatric adverse effects are described with the use of lopinavir/ritonavir nor tocilizumab.

Finally, half of our sample included patients from South America. Ethnic differences in COVID-19 disease (Pareek et al., 2020) and risk of psychosis (Castagnini and Galeazzi, 2016) have been described, but our results should be taken with caution because of the limited sample size and the socio-demographic characteristics of the study population (Chowkwanyun and Reed, 2020).

#### 4.1. Limitations

Sample size was small and we could not retrospectively obtain incidence rates. It was not possible to report complete neurological exams, other inflammatory biomarkers (such as IL-6) and virus PCR in the cerebrospinal fluid. Further follow up of the patients should be also recommended in order to clarify if they remain asymptomatic or develop a mental illness.

#### 4.2. Conclusions

Structured delusions mixed with confusional features were the most frequent psychiatric manifestations observed in the COVID-19 patients studied. In most cases psychotic symptoms could be the result of various pathological mechanisms, which include direct effect of the virus into the CNS, indirect effect (by inflammatory reactions, metabolic disturbances, hypoxia...) and adverse effects of pharmacological treatments used against the virus. Larger studies should be conducted in order to keep exploring this question.

#### CRedit authorship contribution statement

**A. Parra:** Conceptualization, Formal analysis, Writing - original draft, Investigation. **A. Juanes:** Conceptualization, Writing - original draft, Investigation. **C.P. Losada:** Conceptualization, Project administration, Writing - review & editing. **S. Álvarez-Sesmero:** Conceptualization, Resources, Writing - review & editing. **V.D. Santana:** Conceptualization, Resources, Investigation. **I. Martí:** Conceptualization, Investigation. **J. Urricelqui:** Conceptualization, Investigation. **D. Rentero:** Conceptualization, Methodology, Writing - review & editing.

#### Declaration of Competing Interest

None

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