Abstract: This case series reports three middle-aged male patients with no prior history of psychiatric disorders who developed psychotic symptoms with manic characteristics after COVID-19 infection. They presented mystic and paranoid delusions associated with euphoria, logorrhea, insomnia, and bizarre behaviors. Two of them required psychiatric hospitalization and one received corticosteroids. Treatment with antipsychotic medication improved their symptoms in a few weeks. This case series reports the new-onset psychosis probably due to COVID-19 infection. Pathogenetic speculation about the probable causes of COVID-19 psychosis, such as inflammatory reaction and corticosteroid use, was done. Moreover, other probable causes of manic psychosis, such as late-onset bipolar disorder, were also considered and ruled out. There is a need for more research to determine the causality between psychotic symptoms and COVID-19 infection.

Key Words: COVID-19, glucocorticoids, psychotic disorders, mania, inflammation

(J Nerv Ment Dis 2022;210: 724–726)

The COVID-19 pandemic started in Wuhan, China, in December of 2019 (World Health Organization, 2020). At the end of June 2021, it has affected more than 180 million people, and the number of cases in Argentina has reached nearly 4.5 million (Ministerio de Salud Argentina, 2021; World Health Organization, 2021).

Among many complications of COVID-19 infection, neuropsychiatric disorders, including psychosis, have been described (van Vuren et al., 2021). The etiology of psychosis correlated to COVID-19 infection is unknown, but many reports speculate that inflammatory response in CNS and the prescription of corticosteroids may be related to the development of psychosis (Kozato et al., 2021; Sirois, 2003; van Vuren et al., 2021). Moreover, many of the drugs used in intensive care unit in severe cases (such as propofol, fentanyl, midazolam) can potentially induce psychotic symptoms (Burnakis and Berman, 1989; Marchaisseau et al., 2008; Sivanesan et al., 2016).

We present three clinical cases of male adults who developed psychotic symptoms after COVID-19 mild to moderate infection. The patients have no history of psychiatric disorders, and two of them required treatment in a psychiatric inpatient unit.

CASE 1

In May 2021, a 56-year-old man was diagnosed with a COVID-19 infection. He had no history of psychiatric and clinical diseases, and he did not use drugs or alcohol.

During the COVID-19 infection, the patient experienced myalgias, fatigue, stomachache, diarrhea, weight loss, diaphoresis, and insomnia (no more than 3 hours of sleep a day). He has been treated with paracetamol 500 mg every 8 hours.

A month after a COVID-19 infection, the patient suddenly started with a crying crisis and mutism. He communicated with his family only through writing. He developed delusional mystical manifestations (he asked God for permission for everything), insomnia, and bizarre behaviors (he printed a T-shirt with the date June 10, 2021).

The patient was taken to psychiatric consultation and was hospitalized in a psychiatric unit with a diagnosis of mania with psychotic symptoms. He was logorrheic, tachypsic, agitated, and complainant. Pharmacological treatment with haloperidol 15 mg/d (oral), lorazepam (oral) 12 mg/d, levomepromazine 75 mg/d (oral) was indicated. Four days later, the patient was somnolent, without clinical improvement. For this reason, medication was changed to quetiapine 200 mg/d, risperidone 3 mg/d, and clonazepam 2 mg/d (oral). After 5 days, the patient started to improve, with a partial insight of delusional thinking. He was discharged from the hospital at the request of his family.

A week later, the delusional thinking improved but remained with mild residual hypomanic symptoms. The patient continued the pharmacological treatment with quetiapine 100 mg/d, risperidone 3 mg/d, and clonazepam 1 mg/d and remained stable until the end of June on a weekly evaluation basis.

CASE 2

A 57-year-old male teacher, married and with three sons, without a history of clinical and psychiatric symptoms, started on May 13, 2021, with fever and cough. He was diagnosed with COVID-19 infection and treated with paracetamol 500 mg/d every 8 hours and with a puff of budesonide/pratropium every 8 hours. A week later, the patient was diagnosed with bilateral COVID-19 pneumonia with type 1 respiratory failure (hypoxemia without hypercapnia) without oxygen requirement. The patient was admitted to the hospital: he was medicated with meprednisone 40 mg/d for 10 days and an antibiotic regimen of amoxicillin/clavulanate 1 g every 8 hours and clarithromycin 500 mg every 8 hours, both for 7 days.

He was discharged 6 days after the admission and, on the same day, started with crying crises alternated with joy and euphoria. Mystical delusions ("asking for God") and verbosity were also present. A few days later, he developed megalomanic delusional ideas ("I will talk to a famous TV presenter, and I will bring Messi to my city"). An intention to excessive expenses was present, but his family prevented it ("he wanted to get loans to buy irrelevant things"). The patient was hyperactive most of the day, with less need for sleep, and was referred to a psychiatric emergency unit, where a diagnosis of mania with psychotic symptoms was made and ambulatory treatment was indicated. He was started on quetiapine 100 mg/d (oral); a week later, he improved, without logorrhea and euphoria, but still tended to incur unnecessary expenses. A weekly psychiatric evaluation was performed, and he has remained stable with quetiapine 50 mg/d.

CASE 3

A 41-year-old man who works as an employee, without prior history of psychiatric and clinical disorders, was diagnosed on November 27, 2020, with COVID-19 infection. He was isolated in his home and treated with paracetamol 500 mg/d every 8 hours for 4 days. The patient evolved favorably, but a month later was brought by his family to the

*Mental Health Service, Hospital Miguel Capreldon Bolivar; and †Neuropsychopharmacology Division, Psychiatry and Mental Health Department, Hospital Jose de San Martin, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina.

Send reprint requests to Francesco Appiani, MD, Neuropsychopharmacology Division, Psychiatry and Mental Health Department, Hospital Jose de San Martin, Facultad de Medicina, Universidad de Buenos Aires, Avenida Córdoba 2351, 1120, Buenos Aires, Argentina. E-mail: fappiani@fmed.uba.ar.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0022-3018/22/21009-0724
DOI: 10.1097/NMD.0000000000001488
emergency service due to paranoid and mystic delusions of 3 days of evolution. A tendency to aggressive behaviors and disorganized thoughts was also observed. It was decided to refer him to the psychiatric inpatient unit, and he was treated with haloperidol (5 mg), levomepromazine (25 mg), and lorazepam (4 mg) every 8 hours (intramuscular). Because of excessive sedation, haloperidol 5 mg and levomepromazine 25 mg (intramuscular) were indicated every 12 hours. Two days later, the patient was without manic or psychotic symptoms and was discharged with zuclopenthixol depot 200 mg and risperidone 3 mg/d. Two months later, he was without psychiatric symptoms, and medication was gradually decreased until suspension. The patient is being evaluated every 2 weeks, and until June 2021, he has remained stable.

**DISCUSSION**

It is a challenging process in medicine to determine the causality of a process, especially in psychiatry. The cases described all lack a history of psychiatric pathology and developed psychotic symptoms after COVID-19. According to many published reports, there could be a link between COVID-19 infection and the development of psychotic symptoms (Ferrando et al., 2020; Parra et al., 2020; Rentero et al., 2020; Smith et al., 2020; Taquet et al., 2021). Although the causality has not been established, many etiologies may probably be associated with the pathogenesis of psychosis. The inflammatory reaction generated by the COVID-19 might be one such factor (van Vuren et al., 2021).

One hypothesis correlates the systemic inflammation process and the secondary changes in the blood-brain barrier (BBB) with the development of psychotic symptoms (Varatharaj and Galea, 2017). Pollock et al. studied the link between BBB damage and the risk of primary and secondary symptomatology in COVID-19. The higher the risk of neuropsychiatric symptoms. The higher the inflammatory reaction and the prescription of glucocorticoids, opioids, and benzodiazepines (Burnakis et al., 2008; Sirois, 2003; Sivanesan et al., 2016; Taquet et al., 2021). It is critical to highlight that these medicines are frequently associated with delirium, hypoxia, and metabolic disturbances. Delirium may present with psychotic features, but it is always associated with sensorium disturbances that were not present in our clinical series (Beach et al., 2020).

**REFERENCES**

Baldessarini R J, Tondo L, Vázquez GH, Undurraga J, Bolzani L, Yildiz A, Khalsa HK, Lai M, Lepri B, Loich M, Maffeli MP, Salvatore P, Paedea GL, Vieta E, Tohen M (2012) Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World Psychiatry* 11:40–46.

Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N, Fricchione GL, Sirois, 2003; Sivanesan et al., 2016; Taquet et al., 2021). It is critical to highlight that these medicines are frequently associated with delirium, hypoxia, and metabolic disturbances. Delirium may present with psychotic features, but it is always associated with sensorium disturbances that were not present in our clinical series (Beach et al., 2020).

**DISCLOSURE**

The authors declare no conflict of interest.

**CONCLUSIONS**

COVID-19 infection might be associated with the development of psychotic symptoms. The inflammatory reaction, glucocorticoid therapy, and perhaps emotional stress may be related to the pathogenesis of psychosis in COVID-19 infection.

Interestingly, the three patients described had psychotic symptoms after COVID-19 infection, and in two of them, there was no other triggering factor than COVID-19 infection. The patients had no history of psychiatric disorders; all three cases were manic with psychotic features and had a good pharmacological response. After considering and probably ruling out other etiologies, these cases may probably be related to COVID-19 infection.

Finally, more research is needed to determine whether the COVID-19 infection is the cause of psychotic symptoms.

**REFERENCES**

Baldessarini RJ, Tondo L, Vázquez GH, Undurraga J, Bolzani L, Yildiz A, Khalsa HK, Lai M, Lepri B, Loich M, Maffeli MP, Salvatore P, Paedea GL, Vieta E, Tohen M (2012) Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World Psychiatry* 11:40–46.

Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N, Fricchione GL, Sirois, 2003; Sivanesan et al., 2016; Taquet et al., 2021). It is critical to highlight that these medicines are frequently associated with delirium, hypoxia, and metabolic disturbances. Delirium may present with psychotic features, but it is always associated with sensorium disturbances that were not present in our clinical series (Beach et al., 2020).

**DISCLOSURE**

The authors declare no conflict of interest.

**REFERENCES**

Baldessarini RJ, Tondo L, Vázquez GH, Undurraga J, Bolzani L, Yildiz A, Khalsa HK, Lai M, Lepri B, Loich M, Maffeli MP, Salvatore P, Paedea GL, Vieta E, Tohen M (2012) Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World Psychiatry* 11:40–46.

Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N, Fricchione GL, Sirois, 2003; Sivanesan et al., 2016; Taquet et al., 2021). It is critical to highlight that these medicines are frequently associated with delirium, hypoxia, and metabolic disturbances. Delirium may present with psychotic features, but it is always associated with sensorium disturbances that were not present in our clinical series (Beach et al., 2020).

**DISCLOSURE**

The authors declare no conflict of interest.

**REFERENCES**
Parra A, Juanes A, Losada CP, Alvarez-Sesmero S, Santana VD, Martí I, Urricelqui J, Rentero D (2020) Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. Psychiatry Res. 291:113254.

Pollak TA, Dmdarski S, Stone JM, David AS, McGuire P, Abbott NJ (2018) The blood-brain barrier in psychosis. Lancet Psychiatry. 5:79–92.

RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mattham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahli E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Bailie JK, Haynes R, Lndray MJ (2021) Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 384:693–704.

Rentero D, Juanes A, Losada CP, Alvarez S, Parra A, Santana V, Martí I, Urricelqui J (2020) New-onset psychosis in COVID-19 pandemic: A case series in Madrid. Psychiatry Res. 290:113097.

Sirois F (2003) Steroid psychosis: A review. Gen Hosp Psychiatry. 25:27–33.

Sivanesan E, Gitlin MC, Candiotti KA (2016) Opioid-induced hallucinations: A review of the literature, pathophysiology, diagnosis, and treatment. Anesth Analg. 123:836–843.

Smith CM, Komisar JR, Mourad A, Kincaid BR (2020) COVID-19-associated brief psychotic disorder. BMJ Case Rep. 13:e236940.

Taper C (2016) Systemic corticosteroid-associated psychiatric adverse effects. US Pharm. 41:16–18.

Taquet M, Geddes J, Husain M (2021) Six-month neurological and psychiatric outcomes in 236,579 survivors of COVID-19. Lancet Psychiatry. 8:416–427.

van Vuren EJ, Steyn SF, Brink CB, Moller M, Viljoen FP, Harvey BH (2021) The neuropsychiatric manifestations of COVID-19: Interactions with psychiatric illness and pharmacological treatment. Biomed Pharmacother. 135:111200.

Van Winkel R, Stefanis NC, Myin-Germeys I (2008) Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. Schizophr Bull. 34:1095–1105.

Varatharaj A, Galea I (2017) The blood-brain barrier in systemic inflammation. Brain Behav Immun. 60:1–12.

Wang C, Pan R, Wan X, Tan Y, Xu L, McIntyre RS, Choo FN, Tran B, Ho R, Sharma VK, Ho C (2020) A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. Brain Behav Immun. 87:40–48.

World Health Organization (2020) Coronavirus disease 2019 (COVID-19): Situation report, 94, from World Health Organization website. Available at: https://apps.who.int/iris/handle/10665/331865. Accessed March 11, 2021.

World Health Organization (2021) WHO Coronavirus (COVID-19) Dashboard, from World Health Organization website. Available at: https://covid19.who.int/. Accessed March 11, 2021.