

## CASE REPORT

# The complexity of neuropsychiatric manifestations of COVID-19 in South Africa

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SARS-CoV-2 was first identified in Wuhan City, China, in 2019. Initially it was associated with the development of pulmonary disease, but research over the past 2 years has identified effects on multiple systems. Neuropsychiatric manifestations of COVID-19 have been reported in countries around the world, including new-onset psychosis in patients with no personal or family psychiatric history. We present the first case series describing neuropsychiatric manifestations of patients in Johannesburg, South Africa (SA). All four patients presented with their index-episode psychosis, and evidence of COVID-19 infection. The patients had varied psychiatric presentations, from delirium and psychosis to mania, and all responded well to low doses of antipsychotics. One patient had newly diagnosed HIV in addition to COVID-19. Further research is needed to determine the prevalence of neuropsychiatric manifestations in acute SARS-CoV-2 infections in SA.

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SARS-CoV-2 was first identified in Wuhan City, China, in December 2019.<sup>[1]</sup> The virus is predominantly transmitted through respiratory droplets, and has subsequently spread from China throughout the world.<sup>[2]</sup> The first case of COVID-19 in South Africa (SA) was reported on 5 March 2020.<sup>[3]</sup>

Initially, SARS-CoV-2 was implicated in the development of a spectrum of pulmonary disease, ranging from mild upper respiratory tract infection to severe acute respiratory syndrome.<sup>[4]</sup> Subsequently, research showed that various organ systems are affected, including the haematological, cardiac and neurological systems.<sup>[5,6]</sup>

Neurological manifestations of COVID-19 have been identified since 2019, with a study in Wuhan City showing that of 214 patients with severe infection, 36% had neurological, including neuropsychiatric, manifestations such as depression, anxiety, mood disturbances and new-onset psychosis.<sup>[5]</sup> In a UK-wide surveillance study using an online case report notification platform, CoroNerve, psychosis was identified in 10 of the first 153 neuropsychiatric patients surveyed.<sup>[7]</sup> Although data are scarce, psychosis related to COVID-19 has been reported to be associated with confusion and disorganised behaviour, particularly in patients who had been admitted to an intensive care unit.<sup>[8]</sup> Those who present with psychosis typically recover rapidly after treatment with a low dose of antipsychotics.<sup>[8]</sup>

Despite published articles on the neuropsychiatric manifestations of COVID-19 in countries around the world, there are no known data from SA. We report on four patients with COVID-19 and concomitant neuropsychiatric symptoms treated in a specialised psychiatric hospital in Johannesburg.

Ethics clearance was obtained from the University of the Witwatersrand (ref. no. M210491) unconditionally. The research committee at the specialist psychiatric hospital where the patients were treated approved the case report unconditionally. Patient consent was obtained telephonically and documented in the clinical records. It was not possible to obtain written consent, because it was a retrospective case review and because of movement of some of the patients out of the province at the time of manuscript submission.

## Case reports

### Case 1

A 30-year-old woman, unmarried and the mother of one child, presented to an acute hospital in Johannesburg with a 4-day history of sleep disturbances, increased goal-directed activity and auditory hallucinations, as well as persecutory and grandiose delusions. Her symptoms occurred on a background of travelling to Cape Town, where she had probably been infected with COVID-19. This suspicion was based on her report that during July 2020 she had stayed in Khayelitsha, Western Cape Province, the epicentre of COVID-19 infections at that time.<sup>[3]</sup> She had stayed in a small overcrowded house, where several occupants were severely ill with respiratory symptoms (such as coughing and a fever). At that time, COVID-19 testing was not routinely available as it was at the beginning of the first wave in SA during level 4 lockdown.<sup>[9]</sup> The patient had become ill with a fever soon after staying at this house. She returned to Gauteng Province after about 3 weeks, still not feeling entirely well. Soon after arriving in Gauteng by train, she was found in a Pretoria township and was unable to give an account of how she got there. She was confused and disorientated and could not make her way home. She was taken to a local clinic by a community member and was referred to a tertiary hospital in Johannesburg. On arrival, she tested negative for COVID-19. Because of an ongoing psychotic presentation, she was admitted to the acute psychiatric ward. She was re-tested, and the result was negative. The two results were a week apart and were probably false-negative results. After a week in the acute psychiatric ward, the patient was transferred to a specialised psychiatric hospital for further management. She had been started on haloperidol 5 mg nocte at the acute unit initially. She had no previous psychiatric history, no family psychiatric history, no medical comorbidities and no history of substance use. She also had no history of significant head trauma or epilepsy.

On arrival at the specialised psychiatric hospital, owing to a high index of suspicion of COVID-19 infection, the patient was immediately tested and had a positive reverse transcriptase polymerase chain reaction (RT-PCR) result for SARS-CoV-2 using

a nasopharyngeal swab. She presented predominantly with psychosis and impaired awareness, which fluctuated. She was found to be euthymic, but had grandiose ideas. At the time she had no respiratory symptoms and the findings on physical examination were normal. Her psychosis was managed with haloperidol 5 mg nocte. She was treated in a dedicated COVID-19 ward for psychiatric patients at the hospital and completed 14 days of isolation. Investigations at the time included a full blood count (FBC), liver function tests (LFTs), renal function (urea and electrolytes), C-reactive protein (CRP), HIV, syphilis, cerebrospinal fluid (CSF), a urine multidrug test (MDT) and a pregnancy test. All the results were normal or negative, except for a high monocyte count of  $10.2 \times 10^9/L$  and a raised lactate dehydrogenase (LDH) level of 236 U/L. A computed tomography (CT) brain scan and electroencephalography (EEG) were done, and both were normal. Her Mini-Mental State Examination (MMSE) score was 29/30. After the isolation period, she was sent to a general psychiatric ward and weaned off haloperidol. After a week she developed some disorientation, grandiose ideas and psychosis, which fluctuated once again. She was initiated on olanzapine 5 mg nocte which was titrated up to a maximum of 15 mg nocte over a 4-week period. The psychosis persisted for 2 months during her admission. Olanzapine was chosen because of its lower extrapyramidal side-effect profile and mood-stabilising properties. She was discharged from the hospital after 2 months and was followed up at the hospital's neuropsychiatric clinic. She has been weaned off the olanzapine and remains well. A COVID-19 antibody test a month after discharge was positive. She has no cognitive impairment (the MMSE score remained 29/30). However, she still complains of ongoing fatigue. Her final *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) diagnosis was psychotic disorder due to another medical condition (COVID-19).

### Case 2

In January 2021, a 23-year-old woman with no known medical or psychiatric comorbidities presented to a hospital in a rural area in KwaZulu-Natal (KZN) Province with an acute onset of severe headache, confusion and aggression. At the time there was a cluster outbreak of COVID-19 in KZN. She was admitted for a period of 5 days, and discharged on unknown medication. It is not known whether she was tested for SARS-CoV-2 at that time. One month later, she presented to a specialised psychiatric hospital in Johannesburg with a 3-day history of severe headache, confusion, disorganised speech and behaviour, aggression, dysmegalopsia, and bizarre and persecutory delusions. She had no known family history of mental illness, and no history of substance use. She was admitted as an involuntary mental healthcare user for further investigations and management.

On mental status examination (MSE), the patient presented with psychomotor agitation. She was disinhibited and intrusive. She was coherent with persecutory and bizarre delusions and was not objectively hallucinating. The MMSE score was 19/30 with impairment in orientation, recall and attention. She had impaired insight and judgement. The findings on physical, and in particular neurological, examination were normal. A full work-up was done to exclude medical causes of her presentation, and a routine nasopharyngeal swab for COVID-19 RT-PCR was positive. Her white cell count and CRP were normal. She had normal urea and electrolytes, LFTs and thyroid function tests. She tested negative for HIV and syphilis. Her urine MDT was negative. A CT scan of the brain showed a dilated vein of Galen, which was reported as normal. A lumbar puncture was done, and CSF results were normal. After

the isolation period in the hospital's COVID-19 ward, her fluctuating level of orientation resolved, but not the psychosis. She was treated with haloperidol 5 mg nocte, as it had been started at the referring hospital. Because she had no side-effects, the decision was made to continue the treatment and observe for side-effects. All deficits on MSE resolved rapidly. The patient was followed up at the local clinic after discharge, and was continued on the low-dose haloperidol with a plan to wean her antipsychotic with monitoring as an outpatient. She was reviewed at our hospital's neuropsychiatric clinic 2 months after discharge, and remained euthymic and without psychotic symptoms. Her final DSM-5 diagnosis was psychotic disorder due to another medical condition (COVID-19).

### Case 3

In December 2020, a 22-year-old woman, unmarried with no children, was admitted to an acute hospital in Johannesburg with a history of being missing from home for 1 week prior to admission. She was found at a dumping ground in Pretoria, confused and with disorganised behaviour. During the week prior to her disappearance from home, she reported having had symptoms that were highly suggestive of a possible COVID-19 infection, with a sore throat and a fever. She presented with psychotic symptoms including commanding auditory hallucinations, and grandiose and persecutory delusions. She also had maniform symptoms with an irritable mood and increased energy. The patient had no previous psychiatric history and no family psychiatric history. She reported that she consumed alcohol occasionally with no problematic use, and had no history of significant head injury or epilepsy. The patient tested HIV positive during this admission. She had been tested for HIV a month before the admission, and the test was negative.

On admission to the specialised psychiatric hospital, the patient was noted to be talkative although not pressured. Her mood was mildly elevated and remained so for most of the admission, with underlying irritability. Her thought content included grandiose and persecutory delusions, although the thought form was coherent. Findings on physical examination were normal on admission. The patient's nasopharyngeal swab for COVID-19 RT-PCR at the acute general hospital was negative. However, on arrival at the psychiatric hospital she tested positive for COVID-19 antibodies. Her HIV viral load was 19 900 copies/mL and her CD4 count was 488 cells/ $\mu L$ . Syphilis and hepatitis screens were negative. Her liver, renal and thyroid function as well as an FBC, CRP, lipogram and glycated haemoglobin were all normal. A CT scan of the brain and an EEG were normal, with normal CSF. A urine pregnancy test and MDT were negative.

The patient was initially diagnosed with bipolar and related disorder due to HIV, since she was newly diagnosed with HIV on this admission. After her antibody results and a history suggestive of a COVID-19 infection, the diagnosis of bipolar and related disorder due to COVID-19 was added to her differential diagnoses. She was treated with olanzapine 5 mg nocte and lithium 700 mg nocte. Because she had both mood and psychotic features, olanzapine, an atypical antipsychotic, was chosen because of its better side-effect profile. Lithium (a mood stabiliser) was started due to side-effects on sodium valproate. She was also started on a fixed-dose regimen for HIV, tenofovir, lamivudine and dolutegravir. She was lost to follow-up when she returned home to KZN. Her final DSM-5 diagnosis was psychotic and mood disorder due to another medical condition (COVID-19), with a differential diagnosis of psychotic disorder caused by HIV.

**Case 4**

A 36-year-old man was brought to a general hospital casualty department with a 3-day history of confusion, auditory hallucinations and persecutory delusions. Prior to the onset of these psychotic symptoms, he reported a 5-day history of nasal congestion, with associated sweating. He had no previous history of head injury, substance use or epilepsy, and no psychiatric history. His brother was reported to have had one episode of cannabis-induced psychotic disorder, which was not confirmed.

The findings on physical examination were normal, but on MSE the patient was noted to have persecutory delusions with impairments in attention and awareness at the referring hospital. Blood and CSF investigations were done to determine the cause of his delirious presentation. His CRP was raised at 17 mg/L, with a high monocyte count of  $0.85 \times 10^9/L$ . His nasopharyngeal swab for COVID-19 RT-PCR was positive.

The patient was transferred to our psychiatric hospital, where he tested positive for COVID-19 and completed his isolation period, during which he remained physically stable. For the first 4 days of his admission he reported auditory and visual hallucinations, which subsided by day 5 on a low-dose atypical antipsychotic, risperidone 3 mg nocte. He was fully orientated with no impaired awareness on arrival at the specialised psychiatric hospital. The antipsychotic treatment was then tapered down and stopped prior to his discharge, with no resurgence of psychotic symptoms. His final DSM-5 diagnosis was delirium due to another medical condition (COVID-19).

**Case correlations**

The history, physical findings, findings on MSE and results of investigations in the above four cases are compared in Table 1.

**Discussion**

The four cases reported illustrate the presence of psychosis in patients who tested positive for COVID-19 around the time of their first psychiatric presentation, with no prior personal or family psychiatric history, suggesting that their neuropsychiatric symptoms could potentially be a result of COVID-19 (Table 1). Similar findings were illustrated in a UK-wide surveillance study in which psychosis and an altered mental state were associated with COVID-19 infection.<sup>[7]</sup>

Case 3, with HIV, is interesting and somewhat different, and for teaching purposes we thought it would be of value to include it. This patient had typical respiratory symptoms of COVID-19 prior to her psychosis and disappearance from home. She had a documented negative HIV result a month prior to this event, and was antiretroviral treatment naive. The reason for her initial HIV test is not fully known. On admission to the hospital, exposure to COVID-19 was evident as demonstrated by a positive antibody test, although the exact time period of acute infection could not be confirmed. She was also then diagnosed with HIV. The high viral load indicates an infection of recent onset, probably at the time during which she disappeared from home. However, the possibility that she was in the seroconversion phase prior to getting COVID-19 cannot be ruled out. The synergistic effect of the two viruses may have precipitated the delirium and psychosis. Being in the

**Table 1. Comparison of history, physical findings, findings on MSE and results of investigations in 4 patients who presented with neuropsychiatric manifestations of COVID-19**

	Case 1	Case 2	Case 3	Case 4
Age (years)	30	23	22	36
Past psychiatric history	No	No	No	No
Family psychiatric history	No	No	No	Yes (not confirmed)
History of substance use	No	No	No	No
History of head injury	No	No	No	No
Medical comorbidities	No	No	HIV	No
Physical examination	Normal	Normal	Normal	Normal
Delirium on presentation	Yes	Yes	Yes	Yes
Psychosis on MSE	Yes	Yes	Yes	Yes
Mania on MSE	No	No	Yes	No
MMSE	29/30 lost points in attention	19/30 lost points in orientation, recall and attention	24/30 lost points in attention and orientation	-
MOCA	25/30 lost points in visuospatial, attention, language, delayed recall	-	-	19/30 with deficits in visuospatial, attention, language, abstraction and delayed recall
Evidence of SARS-CoV-2	PCR +	PCR +	Antibody +	PCR +
Monocyte count (cells $\times 10^9/L$ )	10.2 (high)	-	-	0.85 (high)
CRP (mg/L)	<10	<10	<10	17
LDH (U/L)	236	-	-	-
HIV	Negative	Negative	Positive	Negative
Viral load (copies/mL)	NA	NA	19 900	NA
CD4 count (cells/ $\mu L$ )	NA	NA	488	NA
CSF	No abnormalities	No abnormalities	No abnormalities	No abnormalities
Inpatient treatment	Olanzapine 15 mg po nocte	Haloperidol 5 mg po nocte	Olanzapine 5 mg po nocte	Risperidone 3 mg po nocte

MSE = mental status examination; MMSE = Mini-Mental State Examination; MOCA = Montreal Cognitive Assessment; PCR = polymerase chain reaction; CRP = C-reactive protein; LDH = lactate dehydrogenase; CSF = cerebrospinal fluid; NA = not applicable; - = not measured.

seroconversion phase initially may have put the patient at increased risk of contracting COVID-19 as a result of an impaired immune system. Manifest symptoms were also present, which the other three patients did not have. Even considering the new HIV diagnosis, it is possible that concomitant COVID-19 infection had an impact on her neuropsychiatric presentation.<sup>[10]</sup>

None of the patients in this case series had a previous personal psychiatric history, although one had a relative who was reported to have had a cannabis-induced psychosis, which was not confirmed, and all had been in good physical health with no comorbidities, suggesting no propensity to any psychiatric illness. All the patients' symptoms resolved relatively quickly on low-dose antipsychotics. None has continued on any psychiatric treatment. One patient was lost to follow-up.

There is increasing evidence of neurotropism of COVID-19,<sup>[5]</sup> and SARS-CoV-2 seems to invade the CNS in various ways. Proposed mechanisms include cell to cell, via the CSF, haematogenous spread, and retrograde axonal transport.<sup>[11]</sup> Although neuropsychiatric presentations are still evolving, as they become characterised they also seem to vary widely.<sup>[11]</sup> A Spanish study showed that 57.4% of people treated for COVID-19 during 2020 had at least one neurological presentation,<sup>[12]</sup> and a large multicentre European study showed varied rates of both neurological and psychiatric presentations following COVID-19 infection.<sup>[13]</sup> What has been difficult to determine in most publications is the absent premorbid histories of both psychiatric and neurological illness or predispositions. There is a short report in the literature of one case of persistent psychotic symptoms following COVID-19 infection.<sup>[14]</sup> COVID-19 is associated with a pro-inflammatory cytokine storm and with varied clinical presentations and raised biological markers. This cytokine storm may explain the delirium and psychosis. Multiple immune signalling pathways are also seen in various psychiatric presentations without the presence of COVID-19, which could further explain the clinical presentation of psychosis precipitated by COVID-19 infection with a present underlying inflammatory state.<sup>[1]</sup>

Our patients had minimal abnormal biological markers commonly seen and monitored in early COVID-19 infection, such as lymphopenia, raised CRP, raised D-dimers, raised LDH and raised interleukin 6 (Table 1). While other biological markers were not tested for, such as autoantibodies to exclude encephalitis, we consider that there was not enough clinical evidence and severe deterioration to include them. Although we cannot definitively say that there is a causal link between COVID-19 infection and psychosis or neuropsychiatric presentations, our cases demonstrate a possible link in the absence of past psychiatric and neurological predispositions to these conditions. Our case reports may have some limitations, namely lack of similar investigations across all cases and missing information on previous medical history for patients who came from outside Gauteng.

As we characterise more cases with neuropsychiatric syndromes and develop better ways of capturing information on our COVID-19 patients that is more comprehensive and holistic, greater understanding of the neuropsychiatric presentations will develop. It may result in a change in the DSM classification, where the neuropsychiatric presentations due to COVID-19 may become recognised as conditions for further research study. Recognising the effects of COVID-19 on both neurological and psychiatric presentations may result in better management of our patients with SARS-CoV-2 infection.

**Declaration.** None.

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1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. *JAMA* 2020;324(8):782-793. <https://doi.org/10.1001/jama.2020.12839>
2. Zhu N, Zhang D, Wang W, et al.; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382(8):727-733. <https://doi.org/10.1056/nejmoa2001017>
3. Brandt K. CT becomes epicentre of COVID-19's third wave. *Eyewitness News*. <https://ewn.co.za/2021/07/30/wc-now-the-epicentre-of-sa-s-covid-19-third-wave> (accessed 24 September 2021).
4. Guan WJ, Ni ZY, Hu Y, et al.; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-1720. <https://doi.org/10.1056/NEJMoa2002032>
5. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalised patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77(6):683-690. <https://doi.org/10.1001/jamaneurol.2020.1127>
6. Nakamura ZM, Nash RP, Laughon SL, Rosenstein DL. Neuropsychiatric complications of COVID-19. *Curr Psychiatry Rep* 2021;23(5):25. <https://doi.org/10.1007/s11920-021-01237-9>
7. Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. *Lancet Psychiatry* 2020;7(10):875-882. [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X)
8. Parra A, Juanes A, Losada CP, et al. Psychotic symptoms in COVID-19 patients: A retrospective descriptive study. *Psychiatry Res* 2020;291:113254. <https://doi.org/10.1016/j.psychres.2020.113254>
9. Abdool Karim SS. The South African response to the pandemic. *N Engl J Med* 2020;382(24):e95. <https://doi.org/10.1056/nejmc2014960>
10. Jassat W, Cohen C, Tempia S, et al. Risk factors for COVID-19-related in-hospital mortality in a high HIV and tuberculosis prevalence setting in South Africa: A cohort study. *Lancet HIV* 2021;8(9):e554-e567. [https://doi.org/10.1016/S2352-3018\(21\)00151-X](https://doi.org/10.1016/S2352-3018(21)00151-X)
11. Fernandes S. Neuropsychiatric sequelae in post COVID-19 illness. *S Afr Psychiatry* 2021;26(Feb):41-46.
12. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurological manifestations in hospitalised patients with COVID-19: A retrospective, observational study from a Spanish population. *The ALBACOVID Registry*. *Neurology* 2020;95(8):e1060-e1070. <https://doi.org/10.1212/wnl.0000000000009937>
13. Dinakaran D, Manjunatha N, Kumar CN, Suresh BM. Neuropsychiatric aspects of COVID-19 pandemic: A selective review. *Asian J Psychiatry* 2020;53:102188. <https://doi.org/10.1016/j.ajp.2020.102188>
14. Lim ST, Janaway B, Costello H, Trip A, Price G. Persistent psychotic symptoms following COVID-19 infection. *BJPsych Open* 2020;6(5):E105. <https://doi.org/10.1192/bjo.2020.76>

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