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Correspondence

Letter to the Editor: New onset psychosis and mania following COVID-19 infection



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1. Introduction

Evidence suggests that acute severe respiratory syndrome coronavirus 2 (SARS-CoV-2) may be associated with neuropsychiatric symptoms, including delirium (Zubair et al., 2020; Rogers et al., 2020). Here we present two case reports of adult patients with COVID-19 infections who presented with severe psychosis and mania with no prior psychiatric history and in the absence of significant medical or pulmonary symptoms and an unremarkable neurological work-up.

2. Case 1

A 49 year old man (Patient-A) with hypertension, hyperlipidemia, and type 2 diabetes mellitus, but no personal or family psychiatric history and no substance use history or smoking, was brought to the psychiatric emergency department (ED) with an altered mental status and bizarre behavior.

Clinical presentation: Patient-A presented with one week of insomnia and two days of altered behavior including confusion, decreased appetite, and grandiosity and making odd statements. Three weeks prior to his ED admission, Patient-A was diagnosed with presumed COVID-19, treated with oral azithromycin, and told to self-quarantine. He later presented to urgent care with a urinary tract infection and was treated with nitrofurantoin. His quarantine ended one week prior to his ED admission. In the ED, Patient-A appeared drowsy, was oriented only to the year, and endorsed hearing voices and delusions of grandiosity. On physical exam he had bilateral lower extremity weakness (proximal > distal) and numbness of the right calf and left anterior thigh affecting his ability to ambulate. Patient-A tested positive for COVID-19.

Clinical management: Patient-A was admitted to medicine for work-up. Complete neurological work-up including brain computed tomography (CT), brain magnetic resonance imaging (MRI), electroencephalogram (EEG), lumbar puncture and urine toxicology were unremarkable (laboratories are presented in Table 1). Over the next 10 days, Patient-A remained disoriented, paranoid, and believed that he was the devil and stated that his family was in danger. He endorsed auditory hallucinations, confabulated episodes of violence at home and experienced insomnia, crying spells, hopelessness, sadness, guilt, inattentiveness, restlessness, ideas of reference, and passive suicidal

ideation. He was treated with haloperidol 2mg as needed for agitation and received trials of olanzapine 2.5mg/day and then quetiapine up to 150mg/day and transferred to inpatient psychiatry for continued care. He remained psychomotor retarded, weak, wheelchair-bound, partially oriented to time and place, and with passive suicidal ideation. Over the following 2.5 weeks, Patient-A gradually improved and antipsychotic medications were tapered off. At discharge, Patient A continued to show residual increased speech latency and psychomotor retardation.

3. Case 2

A 34 year old woman (Patient-B) presented to the ED with altered mental status and new onset of psychosis. She had no prior personal or family psychiatric history, no significant medical or surgical history, and no history of substance use or smoking.

Clinical presentation: Patient-B presented with bizarre behavior including disrobing in front of strangers, talkativeness, insomnia, and persecutory ideas about her landlord. She was carrying a knife, and believed she was being watched. Symptoms started two and half weeks prior to this ED admission when she was first seen in the ED due to severe agitation and anxiety. During the exam, she was screaming, not responding to questions and stated she did not feel safe. At that time, she tested positive for SARS-CoV-2. Chest x-ray and head CT were normal, and she was sent home to self-quarantine. Patient-B had two additional ED admissions due to shortness of breath and anxiety, and later increased paranoia and bizarre behavior including putting hand sanitizer in her food. Throughout these three ED presentations, there was no fever or signs of pneumonia on chest x-ray while tests for SARS-CoV-2 remained positive. Patient-B was sent again to self-quarantine leading to a fourth ED admission due to worsening of psychosis and bizarre behavior. Mental status exam was remarkable for psychomotor agitation, loud pressured speech, irritable mood, labile intense affect, circumstantial thought process, paranoid delusions, and impaired attention and concentration. Orientation was intact. Vital signs were within normal limits as was her physical exam. Urine toxicology was negative. Repeated head CT and chest x-ray were normal. Patient was started on risperidone 1mg at night and was admitted to medicine for a workup of acute altered mental status presumed to be secondary to SARS-CoV-2 infection.

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Table 1
Laboratory and neuroimaging tests.

	Patient-A	Patient-B
Gender	Male	Female
Age	49 yo	34 yo
O ₂ Saturation	100%	100%
RT-PCR SARS-CoV-2	Positive x 2 Negative x 1	Positive x 3
Pulse	86–101	69–88
Respiration	18–20	16–18
Temperature	97.1–98.5	98.2–98.6
Blood Pressure	101/68–127/89	91/60–102/60
CBC	Mild anemia (Hemoglobin 13, normal range for males 14.0–17.4 g/dL), normal WBC	Mild anemia (Hemoglobin 11.4, normal range for females 12.2–15.3 g/dL), Leukopenia (WBC = 3.1, normal range 4.8–10.8 k/uL)
Metabolic Panel	Normal	Normal
D-dimer	>20	Not done
Ferritin (normal range 10–150 ng/mL)	1289	Not done
Cardiac enzymes	Negative	Negative
C-reactive protein	<0.5	<0.5
HIV	Negative	Negative
Syphilis	Negative	Not done in blood negative in CSF
Autoimmune Panel	Negative	Negative
Urine Toxicology	Negative	Negative
EEG	Unremarkable	An EEG showed focal cerebral dysfunction in the right greater than the left frontal regions, with no epileptiform discharges or seizures
Electrocardiogram	Right bundle branch block	Normal
Chest x-ray	Low lung volume, increased interstitial markings	Unremarkable x 2
Urine toxicology	Negative	Negative
Cardiac enzymes	Negative	Negative
Head CT	Unremarkable	Unremarkable x 2
Brain MRI	Unremarkable	Nonspecific foci of T2 hyperintense signal abnormality in the right parietal subcortical white matter
Lumbar puncture/CSF	Protein 57 mg/dL (normal range 10–40mg/dL), reactive to SARS-CoV-2 antibody, negative RT-PCR SARS-CoV-2	Normal chemistry. Negative for HIV, HSV, VDRL, enterovirus PCR, oligoclonal bands, cryptococcal antigen, fungal and bacterial cultures, as well as autoimmune panels

*Complete Blood Count (CBC), Cerebrospinal Fluid (CSF), White Blood Cells (WBC), Human immunodeficiency virus (HIV); Herpes simplex virus (HSV), Venereal disease (VDRL).

Clinical management: Neurological work-up: Brain MRI showed non-specific T2 hyperintensities and a lumbar puncture was unremarkable. An electroencephalogram showed greater focal cerebral dysfunction in the right frontal region than the left, with no epileptiform discharges or seizures. Detailed laboratory test results are included in Table 1. Empiric treatment with acyclovir was initiated for possible encephalitis and risperidone was titrated up to 1mg twice daily. Patient-B continued to present with sleep disturbance, agitation, pressured speech, and paranoid ideation. After ten days, the patient was admitted involuntarily to a specialized COVID-19 positive psychiatric inpatient unit. A week after admission to inpatient psychiatry, manic symptoms resolved. Paranoid ideas and delusions remained though were more reality based. She was discharged with psychiatric outpatient follow-up.

4. Discussion

These cases illustrate an association of neuropsychiatric symptoms with COVID-19 infection, in the absence of personal or family history of psychiatric illness, as well as the absence of hypoxemia, cerebral infarction or significant pulmonary involvement. While vasculitis and encephalitis are possible mechanisms, work-up for both cases was not fully consistent with these diagnoses. Relatedly, a recent meta-analysis by Rogers et al., reported high rates of delirium, depression, and anxiety among patients with COVID-19 patients and possible residual executive dysfunction (Rogers et al., 2020). A nation-wide surveillance study from the UK, using an online case report portal, yielded 23 cases (18%) with new onset neuropsychiatric syndromes, including 10 cases with psychosis, 6 cases with dementia-like symptoms, and 4 cases with affective disorders (Varatharaj et al., 2020). A possible mechanism may involve immune system activation and its effect on the CNS. Importantly, inflammatory processes, including activation of the kynurenine pathway, have been implicated in a wide range of psychiatric presentations including psychosis, bipolar, depression and suicide. Such relationships have been documented in the absence of elevated blood CRP levels (Bradley et al., 2019; Reus et al., 2015; Tanaka et al., 2017; Schwarcz and Pellicciari, 2002; DeWitt et al., 2018; Troyer et al., 2020). Follow-up studies should be carried out on the course, duration and treatment of psychiatric sequelae in these patients.

Declaration of competing interest

All authors declare no conflicts of interest.

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Rachel Noone, Johanna A. Cabassa, Laura Gardner, Bruce Schwartz,
Jonathan E. Alpert
Department of Psychiatry and Behavioral Sciences, Albert Einstein College of
Medicine, Montefiore Medical Center, Bronx, NY, USA

Vilma Gabbay*

*Department of Psychiatry and Behavioral Sciences, Albert Einstein College of
Medicine, Montefiore Medical Center, Bronx, NY, USA
Department of Clinical Research, Nathan S. Kline Institute for Psychiatric
Research, Orangeburg, NY, USA*

* Corresponding author. Psychiatry Research Institute of Montefiore
Einstein, Pediatric Mood and Anxiety Disorders Program, Albert
Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY,
10461, USA.
E-mail address: vilma.gabbay@einsteinmed.org (V. Gabbay).