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CASE SERIES OF FIRST-TIME MANIC EPISODE ASSOCIATED WITH SARS-COV-2 INFECTION

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INTRODUCTION

COVID-19 began as a respiratory disease at the end of the year 2019 but soon after it was seen that many clinical manifestations accompany SARS-CoV-2 infection (Machhi et al. 2020, Afrisham et al. 2022). The virus affected nearly every system including the central nervous system (CNS). Numerous neuropsychiatric symptoms were noted and published since the emergence of the disease (Rogers et al. 2020, da Silva Júnior et al. 2022, Zia et al. 2022). Psychotic disorders found themselves an extensive place in psychiatric literature, probably because positive psychotic symptoms such as delusions and hallucinations are more remarkable when compared with affective symptoms (Gokcay & Belli 2022, Gullulu et al. 2022, Zia et al. 2022). Since the beginning of the pandemic, a great number of psychotic disorder cases associated with SARS-CoV-2 have been published and it has been demonstrated that SARS-CoV-2 is able to cause both first-episode psychotic attack and relapse of a psychotic disorder. As shown by plenty of researchers, the virus is also known to cause affective and anxiety symptoms (da Silva Júnior et al. 2022, Zia et al. 2022). In the psychiatric literature, it is well shown that SARS-CoV-2 infection is associated with an increased rate of anxiety disorders. Additionally, depressive disorders are seen at higher rates. Affective symptoms also include manic symptoms, although these cases are fewer in number (Sabe et al. 2022, Haddad et al. 2021, Park et al. 2021, Varsak et al. 2021, Del Casale et al. 2022, Sen et al. 2021, Russo et al. 2022). Hereby, we present three female patients with first-time manic episodes after SARS-CoV-2 infection who were treated in the psychiatry ward for female patients. The first case is a middle-aged female with a first-time manic episode whereas the others have depressive episode history.

CASE PRESENTATION

Case 1

Our first case was a 56-year-old female, the youngest of seven siblings. She had a high school degree and was not working. She was divorced and had 2 children. When admitted to our psychiatric emergency department, she had been experiencing the following symptoms for approximately 15 days: a decrease in the need for sleep, talkativeness, screaming purposelessly, throwing belongings to the street through windows, and thinking that the journalists were somehow communicating with her via television. She had come to our psychiatric emergency department with an ambulance within the week. At one admission, she was assessed as having a dissociative disorder and at the other as hypomania. She had a history of fibromyalgia for which she was using duloxetine 60 mg/day. At her last admission, duloxetine was ceased and she was prescribed olanzapine 10 mg/day for hypomanic symptoms. Since she was nonadherent to prescribed medications and had dangerous behaviors she was hospitalized.

At the time of hospitalization, physical and neurological examinations of the patient were evaluated as normal. She was conscious, oriented to time, place, and person, and cooperative. Her self-care was low. Though she was talkative, she wasn't making eye contact. Her affect and mood were angry and irritable, respectively. Her thought content was delusional with persecutory and grandiose themes. She had auditory and visual hallucinations. Her judgment and insight were poor. Complete blood count, biochemical parameters of the serum, thyroid hormone profile, and urinalysis were within normal range. Urine psychoactive drug analysis resulted in negative. She had no history of psychiatric diagnosis and treatment except for duloxetine which she was using for the diagnosis of fibromyalgia. She also had no family history of psychiatric disorders.

After hospitalization, a nasopharyngeal swab was collected and a polymerase chain reaction (PCR) test for SARS-CoV-2 was carried out as she was coughing, and she was diagnosed with COVID-19. She was isolated for ten days and in this time frame, she was given enoxaparin 4000 IU/day subcutaneously. On the tenth day, the PCR test was redone, the isolation and enoxaparin treatment were stopped as the result was negative. For the treatment of psychiatric symptoms, the patient was given haloperidol 20 mg/day and biperiden

10 mg/day via intramuscular way. After having been more cooperative, parenteral medications were stopped gradually, risperidone 2 mg/day p.o. and sodium valproate 750 mg/day p.o. were initiated. Her risperidone dose was increased to 8 mg/day p.o. gradually and biperiden 4 mg/day p.o. was started as her treatment for four weeks as an inpatient. At the same time, the valproate dose was adjusted to 1000 mg/day according to the blood level of the medication. She was discharged from the hospital after her complaints were resolved.

Case 2

The second patient we present here was 27 years old female. She was a university student and wasn't working. She was not married nor had a child. The patient was living with her mother, father, and three younger siblings. When admitted to our emergency department, it was learned that her complaints had begun seven months before with weeping causelessly, sleeplessness, talking to herself, impulsive behaviors, and suicidal thoughts. These symptoms were evaluated to be a part of a depressive episode at another psychiatry department. She was prescribed fluoxetine 20 mg/day, risperidone 1 mg/day, and quetiapine 125 mg/day, however, she didn't take her medications. In time, her episode remitted, but one month before her admission to our hospital manic symptoms emerged. As aggressive behaviors were added 5 days prior to her admission, she was hospitalized for treatment.

Physical and neurological examinations of the patient were normal at hospitalization. The mental status of the patient was as follows: She was conscious, oriented to time, place, and person, and cooperative. Her self-care was average. Her mood was irritable and her affect was annoyed and nervous in accordance with the mood. The speech rate of the patient was increased. There were no perceptional disturbances like hallucination or illusion. In thought content, no delusions or overvalued ideas were detected. Her attention and concentration were decreased, memory was intact. Her judgment and insight were poor. Complete blood count, biochemical parameters of the serum, thyroid hormone profile, and urinalysis were normal, except for C-reactive protein, which was 6.7 mg/dL. Psychoactive substance analysis of urine resulted negative. She had a history of two depressive episodes, one of them was seven months before hospitalization which is explained above and the other was four years before for which she had no treatment or referral to the hospital. No family history of psychiatric disorder was noted.

At admission, she had respiratory symptoms; thus, computerized tomography of the thorax was requested which was in favor of COVID-19. A PCR test resulted positive and she was isolated. Psychiatric treatment was started with intramuscular haloperidol 20 mg/day and biperiden 10 mg/day, and sublingual lorazepam 3 mg/day for the manic episode without psychotic features she was in. On the fifth day of hospitalization, she was still nonadherent to treatment and her creatine kinase was elevated. Intramuscular treatment was stopped and with the consent of the patient's family electroconvulsive therapy (ECT) was commenced. In total, seven ECT sessions were applied. During her follow-up as an inpatient, lithium and aripiprazole were begun. Gradually, the doses were increased to 900 mg/day for lithium and 15 mg/day for aripiprazole. After six weeks of inpatient treatment, she was discharged as her symptoms waned completely.

Case 3

A 51-year-old female with a history of depressive disorder for 15 years and usage of duloxetine 60 mg/day was admitted to the psychiatric emergency department with complaints of aggression and decreased need for sleep. She was also on metformin 100 mg/day for the diagnosis of diabetes mellitus type II. After her admission, she was hospitalized for treatment. At hospitalization, the physical and neurological examination didn't result in abnormal findings. In her psychiatric examination, she was conscious, oriented, and cooperative. Self-care was sufficient. Her mood was euphoric and her affect was labile. Her psychomotor activity, including speech rate, was elevated. She had mystical, persecutory, and paranoid delusions. There was no hallucination of any modality. Attention and concentration were decreased. Her judgment and insight were insufficient. Complete blood count, biochemical parameters of the serum, thyroid hormone profile, and urinalysis were normal and urinal psychoactive substance analysis was negative. There was no family history of psychiatric disorder. From the medical records and anamnesis, it was detected that she had a positive test result for SARS-CoV-2 PCR one month before her hospital admission. She had taken no specific treatment for COVID-19. She was diagnosed with bipolar disorder and given haloperidol 20 mg/day and biperiden 10 mg/day intramuscularly. After her adherence to psychiatric treatment was enough, parenteral treatment was stopped, then aripiprazole 10 mg/day and sodium valproate 750 mg/day p.o. were started. Under this treatment, affective and psychotic findings faded, and in her third week in the hospital, she was discharged with the mentioned treatment regime.

DISCUSSION

Hereinabove, we presented three patients: the first one had a first-time manic episode with psychotic features and no prior psychiatric history, the second one had a first-time manic episode without psychotic features and with prior depressive episodes but no treatment and the last one had a first-time manic episode with psychotic features and prior depressive episodes with treatment. As seen, the cases had different psychiatric history but the first-time manic episode was common.

The literature has several different approaches for the explanation of neuropsychiatric symptoms. To begin with, the COVID-19 pandemic caused unprecedented psychological distress, chiefly for the elderly who were not able to use technological devices such as smartphones or computers. This kind of distress may be the reason of COVID-19 induced mania as stated before (Del Casale et al. 2022, Sabe et al. 2022, Varsak et al. 2021, Iqbal et al. 2021). The second hypothesis of COVID-19-induced mania is the retrograde invasion of frontal areas of the cerebrum by the virus via the olfactory nerve (Russo et al. 2022, Sen et al. 2021). Although there exist two electroencephalography studies that show frontal dysfunctions, this hypothesis necessitates further support (Russo et al. 2022). Thirdly, two associated mechanisms are blamed for the induction of manic episodes after COVID-19: neuroinflammation and autoimmunity. Notably, autoimmunity is thought to be responsible for the cases that develop manic symptoms sometime after SARS-CoV-2 infection (Russo et al. 2022). Neuroinflammatory processes have a massive importance in etiological studies in psychiatry and COVID-19-induced cases are no exception. Various studies show that neuroinflammation might be the key to comprehending mechanisms behind this induction (Rogers et al 2020, Varsak et al. 2021, Uvais & Moideen 2022). After SARS-CoV-2 infection, cytokines such as interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α increase as peripheral inflammatory markers, furthermore IL-6 and TNF-α are also enhanced in mania (Russo et al. 2022, Varsak et al. 2021). Besides, neuroinflammation probably disrupts the blood-brain barrier which causes direct involvement of viral activity in CNS (Del Casale et al. 2022, Haddad et al. 2021, Park et al. 2021, Iqbal et al. 2021). Neuroinvasion of the relevant structures in CNS by SARS-CoV-2 then causes psychiatric symptoms. As known, the virus penetrates cells after binding the angiotensin-converting enzyme-2 (ACE-2) receptor, presumably, this activity leads to a further increase of cytokines and thus creating a vicious cycle (Rogers et al 2020, Sen et al. 2021). Another proposed mechanism for the direct activity of SARS-CoV-2 in CNS is via infecting macrophages before entering cerebrospinal fluid (Haddad et al. 2021). Lastly, manic symptoms may follow COVID-19 treatment. So-called "iatrogenic" manic symptoms were particularly seen after COVID-19 treatment with steroids, other agents like chloroquine are also known to trigger these symptoms (Russo et al. 2022, Del Casale et al. 2022, Iqbal et al. 2021). In summary, SARS-CoV-2-associated manic states may be the result of psychological distress, retrograde invasion of the CNS via olfactory nerve by the virus, autoimmune and neuroinflammatory processes, the direct effect of the virus on neurons, and medications used against the virus. None of the hypotheses explained above elucidate manic symptoms alone. There seem to be close and complex interactions between these. We think that our patients have manic symptoms as a result of this interplay. For example, our first and third cases are middle-aged women, and particularly for these cases psychological distress might have played an important role in the etiology of the manic episode. It is possible to further speculate that both patients have chronic diseases, fibromyalgia and diabetes mellitus respectively, that generate a pro-inflammatory state.

CONCLUSION

Remarkably, all cases we presented here had a different psychiatric history. We assume that SARS-CoV-2 infection, per its multifaceted activity, causes manic symptoms in different contexts. It is crucial to conduct neuroimaging and electrophysiological studies to further illuminate the intricate connections between etiological factors and clinical consequences.

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Filiz Kulacaoglu, Onur Toktamis & Metin Aslan: study design, data collection, first draft, approval the final manuscript.

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