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Case Series

Psychiatry/Mental Health Section

Neuroleptic Sensitivity in Psychotic Patients on Stabilised Doses of Psychotropics during Coronavirus Infection: A Case Series

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ABSTRACT

The emergence of the coronavirus pandemic has transformed into one of the significant health crises faced by the modern era. Its effects are not just limited to the respiratory system, but detrimental effects on the cardiovascular and neurological systems are also known to occur. While neurological complications such as encephalopathies and stroke are common, the neuropsychiatric effects are mostly described in terms of psychological effects only. The effect of coronavirus on both the pharmacodynamics and pharmacokinetics of various psychotropic medications remains debatable. The present case series aimed to highlight a rare and novel finding of the occurrence of neuroleptic sensitivity in three patients (three male patients) with psychotic illness who were previously on a well-adjusted dosage of psychotropic medications after they suffered from a coronavirus infection. It is only over the years, in the aftermath of the pandemic, that the serious and long-term neuropsychiatric complications and pharmacokinetic changes associated with coronavirus infection will be realised. Therefore, it is advisable to exercise caution when using higher doses of psychotropic medications, considering the increase in neuroleptic sensitivity.

Keywords: Coronavirus disease-2019, Neurolepsis, Psychosis, Substance use/addiction

CASE SERIES

Case 1

A 23-year-old male, a known case of bipolar affective disorder, currently in mania with psychotic features, presented to the Outpatient Department (OPD) with complaints of inflated self-esteem, grandiosity, suspiciousness, and increased energy levels. The patient also had a co-morbid cannabis dependence pattern for the past two years. There was nil significant past medical history. The patient was hospitalised and received six sessions of modified Electroconvulsive Therapy (ECT). He was discharged with complete remission on a regimen of divalproate sodium 1000 mg, risperidone 8 mg, trihexyphenidyl 4 mg, lithium carbonate 900 mg, and lorazepam 2 mg.

After two months, the patient presented with a sudden onset of rigidity in all four limbs, tremors in the upper limbs and tongue, increased salvation, and difficulty in deglutition, associated with autonomic disturbances such as tachycardia and a mild grade fever. Investigations revealed mild leukocytosis (12,000/mm) and elevated creatine kinase levels (2487 U/L). The patient was admitted to the high dependency unit, and all psychotropic medications were withheld. Intramuscular promethazine 50 mg was administered thrice a day over two to three days, leading to gradual improvement in Extrapyramidal Symptoms (EPS). However, on the third day, the patient developed altered sensorium and a decrease in oxygen saturation levels, dropping to 80%. Suspecting Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) infection, the patient underwent Reverse Transcription-Polymerase Chain Reaction Test (RT-PCR), High-Resolution Computed Tomography (HRCT) of the chest, and Magnetic Resonance Imaging (MRI) of the brain. The patient tested positive for Coronavirus Disease-2019 (COVID-19) infection, with HRCT Chest findings suggestive of a Coronavirus Disease-2019 Reporting And Data System (CO-RADS) score of 5 [1]. The MRI brain study showed normal findings. The patient subsequently recovered from the COVID-19 infection and continued to receive regular follow-up for his psychiatric illness without any complications.

Case 2

A 32-year-old male, known to have a mental and behavioural disorder due to the use of multiple substances (opioids, benzodiazepines, and antihistamines) for the past 10 years, developed opioid withdrawal symptoms, including abdominal cramps, body aches, excessive lacrimation, sweating, opioid craving, and subsequent deaddiction regimen. The patient tested negative for SARS-CoV-2 upon admission from the emergency department. During the hospital stay, he developed suspiciousness and fearfulness, leading to the administration of an opioid substitution regimen consisting of naloxone 0.5 mg plus buprenorphine 2 mg, along with risperidone 4 mg and trihexyphenidyl 2 mg for psychotic symptoms. After an initial stabilisation period of one week, the patient was shifted to a deaddiction centre. Within eight days of being transferred, the patient experienced drug-induced EPS such as severe rigidity, excessive salivation, tremors in both upper extremities, slurred speech, and fluctuating sensorium. All psychotropic medications were immediately discontinued, and the patient received intramuscular injection of promethazine 50 mg, along with oral trihexyphenidyl for three days until the drug-induced EPS improved. Subsequently, the patient was transferred to a high dependency unit, where a repeat RT-PCR test came back positive. The HRCT chest scan showed a CO-RADS score of 4, and the brain MRI revealed old lacunar infarcts [1]. The patient was then shifted to a COVID-19 care centre, where patient made a full recovery before being transferred back to the deaddiction centre for further management.

Case 3

A 23-year-old male, a follow-up case of paranoid schizophrenia for four years, presented to the OPD. He has co-morbid cannabis dependence and is being treated with clozapine 400 mg, after two failed trials with antipsychotics. Additionally, the patient was taking aripiprazole 15 mg and fluvoxamine 150 mg as an augmentation strategy for obsessive compulsive symptoms. The patient had been in remission until August 2020 when he contracted asymptomatic COVID-19 infection, which recovered without hospitalisation. The patient continued taking his psychotropic medications during

the viral infection. However, during the convalescence period, he visited the OPD due to giddiness resulting in a fall and fracture of his left ankle. The patient also experienced tremors and rigidity in both upper limbs. His vital signs were stable, and there were no autonomic disturbances. After a referral to a neurologist, an MRI of the brain and an electroencephalogram were performed, both of which had normal findings. The patient was advised to gradually taper the dose of clozapine to 200 mg, aripiprazole to 5 mg, and fluvoxamine to 50 mg. Subsequently, his giddiness improved completely, and the rigidity and tremors disappeared. However, patient experienced a relapse in psychotic symptoms, which was managed by slowly optimising the clozapine dose to 200 mg and increasing the aripiprazole dose to 15 mg over the next few weeks.

DISCUSSION

The emergence of the coronavirus pandemic has transformed into one of the most unprecedented and significant health crises faced by the modern era. Since its first reporting in November 2019 in Wuhan, Hubei Province, China, to its global dispersion over a short span of time, there is a major mortality risk associated with the involvement of the respiratory system, leading to extensive lung damage. It also affects other systems such as cardiovascular, renal, and neurological, leading to a high morbid risk both during post and COVID-19 infection [2].

Various neurological symptoms, including encephalitis, encephalopathies, ischaemic stroke, post-viral complications such as disseminated encephalomyelitis, and the peripheral Miller-Fisher variant of Guillain-Barre syndrome, have been observed to occur secondary to the infection [3,4]. This substantiates that the novel virus is neurotropic in nature and has neuroinvasive potential [5]. The propensity of the virus to cross the blood-brain barrier can be stated as one of the possible mechanisms of invasion into the brain. The interference of the coronavirus with the pharmacokinetics of drugs might lead to an increase in the adverse effects profile in those who were previously well stabilised on specific doses of psychotropic drugs during and after the period of viral infection [6].

The central nervous system invasion of the SARS-CoV-2 virus has been postulated based on a similar analogy of neurotropism in other coronaviruses such as SARS-CoV-1, Middle East respiratory syndrome coronavirus (MERS-CoV), and OC43. The virus binds to the Angiotensin-Converting Enzyme-2 (ACE-2) receptor, found in the lungs, pericytes, and the smooth muscle cell wall in the brain, through its structural spike protein and replicates with the help of proteases such as Transmembrane Serine Protease (TMPRSS) 11A1B, cathepsin B and L, and spike-like protein furin [7]. ACE-2 also has a significant co-expression link with Dopa Decarboxylase (DDC), which is a major enzyme in the synthesis of dopamine and serotonin and may alter these pathways (culprit by association strategy) [8]. Alteration in dopamine and related pathways such as the nigrostriatal pathway during coronavirus infection can precipitate EPS in patients who are in remission on psychotropic agents.

The SARS-CoV-2 infection is known to increase D1 and D2 receptors, which in turn increases dopamine, causing downregulation of the immune system (IL-6 and IL-8) via lymphocytes, cytokines, etc., [9,10]. This may lead to a cytokine storm, inducing endothelial inflammation of peripheral vessels, causing a leak in the blood-brain barrier and facilitating the dissemination and entry of the virus into the brain, facilitating more drug entry into the brain [4]. In patients who have concomitant substance abuse such as nicotine, alcohol, cannabis, and opioids, COVID-19 infection might heighten the immunosuppressive action, implying the possible occurrence of an inflammatory reaction and, therefore, a leakage in the blood-brain barrier. This may further lead to excess free drug entry into the brain [11].

In another interesting hypothesis by Braak et al., neurotropic viruses such as SARS-CoV-2 invade the brain through the olfactory or gastrointestinal route and initiate the neurodegenerative process through alpha-synuclein (known to cause parkinsonian symptoms), which then turns into a promiscuous binder and can be transmitted in a prion-like fashion in the substantia nucleus pars compacta [5,12]. Available literature also suggests that the emergence of COVID-19 infection is associated with altered metabolism in the body, which might increase the entry of free drugs into the nervous system, causing various adverse effects [13,14].

The present case series aimed to highlight the effects of SARS-CoV-2 viral infection on psychiatric patients who were maintaining symptomatically well on prescribed psychotropic medications without any side effects. The sudden emergence of EPS during COVID-19 infection in cases A and B can be explained through the hypothesis of the probable involvement of increased D2 receptors leading to immune dysregulation and altered metabolism of the body, causing a leaky blood-brain barrier and free drug entry into the brain.

Delayed or long-term effects and reactivation of infection due to coronavirus are not uncommon, leading to readmissions and complications after recent infection. In case 3, the patient developed EPS and giddiness soon after recovery from COVID-19 infection, probably due to the initiation of a neurodegenerative process during viral infection or a possible increase in receptor sensitivity. However, the definitive etiology remains debatable. Furthermore, all three patients were predominantly using substances of abuse, predominantly cannabis and opioids, in a pattern of dependence, which could have in turn led to immunosuppression. Therefore, their use might contribute to both the causation of viral illness and subsequent complications associated with their use.

CONCLUSION(S)

The aftermath of coronavirus infection will unfold in the years to come. The novelty of the present case series highlights the challenges clinicians might face while treating the neuropsychiatric conditions that arise in the post-coronavirus pandemic. The authors intend to emphasise the need for cautious dosing of psychotropic medication in patients infected with COVID-19 during the pandemic. Slow and step-wise optimisation of psychotropics is advisable in the post COVID-19 era to avoid serious drug-related adverse reactions due to a possible increase in neuroleptic sensitivity.

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