Title: Psychomotor symptoms, cognitive impairments and suicidal thoughts after COVID-19 infection: a case report and the possible allostatic mechanism

Running Title: Neuropsychiatric symptoms after COVID-19

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Informed consent of the patient was obtained after explanation. The authors are responsible for the written manuscript.

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Psychomotor symptoms, cognitive impairments, and suicidal thoughts after coronavirus disease 2019 infection: A case report and possible allostatic mechanism

ABSTRACT

Although neuropsychiatric manifestations are common in survivors of coronavirus disease 2019 (COVID-19), the pathophysiology is not yet elucidated. Here we describe the case of a geriatric inpatient who developed postCOVID depression with psychomotor retardation, anxiety, hopelessness, executive function problems, and suicidal ideations. The language problems and cognitive impairments coemerged with the motor problems. We propose a mechanism associated with problems in energy prediction and regulation in which the coronavirus infection, which causes neuroinflammation and viral activity in the nervous system, interferes with the reward pathway and sensory prediction process. Sigma-1 receptor agonists such as sertraline may regulate energy expenditure and, thus, be beneficial to the process. The treatment improvements in our patient included those in the autonomic nervous system, activity, and circadian rhythm.

INTRODUCTION

Survivors of coronavirus disease 2019 (COVID-19) survivors often develop psychiatric manifestations such as depression, fatigue, anxiety, sleep disorders, and neuro-
cognitive impairments(1, 2). Troyer et al.(3) hypothesized that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affect the central nervous system (CNS) through biological pathways implicated in suicidal behaviors, including the renin-angiotensin system, inflammation system, and nicotine receptors. However, the clinical presentations and underlying pathophysiology have not yet been elucidated. Herein, we illustrate a hypothetical mechanism and describe a relevant case.

CASE REPORT

We present the case of a 68-year-old married woman who had lived with her husband for >30 years and did not have any children. The patient and her husband adopted stray cats, for which she was responsible, and she also performed household tasks including cleaning, cooking, and managing the family's finances. She was healthy and reported taking no medications for any physical conditions before COVID-19. She did not have a psychiatric history before COVID-19 and had completed the three-dose series of the Moderna COVID-19 vaccine. She developed COVID-19 3 months before her psychiatric hospitalization during the period of predominant SARS-CoV-2 omicron-type variant. She reported previously coping well with stress and no major life changes or stressful life events except for the COVID-19 pandemic at that time. After recovery, the patient started to develop a depressed mood, as well as disrupted sleep and
anhedonia. While she reported having previously been very diligent and decisive, she became anxious, could not perform her previous daily routines, and could not make decisions. She also complained of blunted emotional response, making her unable to cry after her cat died.

The patient first presented to a local clinic and was administered alprazolam for her anxiety. However, the condition worsened persistently. She and her husband, who relied on her to perform most of the household tasks, began to feel hopeless. She was experiencing intense feelings of depression and sought help at our outpatient clinic. Although she was prescribed antidepressants (Fig 1a), her condition did not improve. Her functional decline was quite prominent and her speech became weak and murmur-like. She had difficulty forming full sentences when spoken to. Her husband became distressed and asked for rapid adjustment in her medications. After he saw her going to the roof intending to jump off the building, she was hospitalized in the psychiatric ward for safety reasons. After admission, the patient received meticulous monitoring for any adverse effects of the medications. At admission, she expressed suicidal ideations but could not describe the symptoms clearly. A psychological assessment was also performed for suspected major depressive disorder with anxious features and long COVID. The patient could not finish the test and stopped to rest after some unsuccessful trials. Although her limbs seemed freely moveable, her motor
coordination was slow and occasional Parkinson-like tremors were noted. She finished the Mini-Mental State Examination with great difficulty; however, the results showed only mild impairment (27/30). Blood examination findings revealed a low vitamin D3 level, which was corrected. The laboratory data are shown in Table 1. Her problems with initiating and performing procedural motor performance were consistent with the manifestations often seen in patients with basal ganglia lesions. However, no such lesions were observed on brain computed tomography (CT). The electroencephalogram also showed no significant abnormalities.

Upon admission, the patient was administered antidepressants, hypnotics, and atypical antipsychotics (Fig 1). However, her sleep problems and psychomotor retardation persisted. Therefore, sertraline (100 mg daily) was gradually added. After 3 weeks of treatment, she started to talk with fluency. She reported feeling less indecisiveness, a less depressed mood, and could see a future with some hope. We also observed improved activity and circadian rhythm. Suicide ideation sometimes existed but she reported that was not an impediment. The patient was then discharged and she received outpatient follow-ups. No more depressed mood nor suicidal attempts were noted during the follow-up. Her executive function and memory returned to normal levels at follow-up. Besides doing housework, she started to volunteer as a church pianist and could memorize many new gospel songs.
During the hospitalization, the patient underwent Holter monitoring to record 24-h electrocardiography data during the first month of treatment and 1 month later. An analysis of linear heart rate variability (HRV) was conducted, focusing on metrics such as the average normal-to-normal (NN) interval, standard deviation of NN intervals (SDNN), and root-mean-square of the successive differences between adjacent NN intervals (RMSSD), according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology guidelines. We observed increased RMSSD and SDNN after treatment, along with improved depression and anxiety (Figs 1 and 2). These findings may imply better parasympathetic regulation and a more adaptive autonomic nervous system. The HRV fluctuations and diurnal change were restored after the treatment. The improvement in circadian patterns is shown in Fig 2.

**DISCUSSION**

In the absence of previous psychiatric illness and medical comorbidities, the co-occurrence of neuropsychiatric changes following COVID-19 in the present case drew our attention. The fatigue, indecisiveness, and anhedonic symptoms were new-onset during the SARS-CoV-2 infection and persisted and worsened, with suicidal thoughts occurring approximately 3 months later. In old concepts of depression, anxiety and
neuro-vegetative symptoms and suicide are different subtypes. However, differences in phenomenology such as motor symptoms and suicidality are observed in postCOVID depression(4). Without strongly expressing sadness, our patient had anxiety, executive function problems, cognitive deficits, and suicidal ideation. In addition, the language problems and cognitive impairments coemerged with the motor problems. Before the prescription of medications such as mirtazapine and quetiapine, the patient was already experiencing cognitive impairment. However, after a thorough examination of her entire medical history and recovery process, it is unlikely that these medications were the cause of her cognitive disorder. We considered several possible diagnoses, including major depressive disorder with anxious distress, neurocognitive disorder, and generalized anxiety disorder; however, none of these disorders explained her inconsistent clinical picture or the lack of response to treatment in the outpatient clinic.

Therefore, we can inspect the phenomenon from a different viewpoint considering the brain’s predictive regulation of the body. The major role of the brain is to anticipate the metabolic needs of the body and meet these needs before they arise (termed allostasis); additionally, emotions are constructed to coordinate bodily systems for efficient energy regulation in an ever-changing but only partly predictable world(5, 6). When an organism moves, the brain evaluates the required energy expenditure and compares the expected reward after the move. In our patient, the changes in actions
and decisiveness preceded the sadness. Motor actions, emotions, and impaired circadian rhythm and autonomic dysfunctions may all be related to the disrupted predictions. Predictions are constantly formed and reorganized according to environmental feedback. The autonomic profile of the current patient suggested that ineffective energy management arising from impaired allostasis might be closely linked to the psychopathology. COVID-19 causes neuroinflammation and viral activity in the nervous system and interferes with the reward pathway and sensory prediction process(7), which may result in reward learning deficiency and the aberrant estimation of motor and energetic costs. Patients tend to report reduced cognitive performance recovery from COVID-19(8). In these patients, the heterogeneous cognitive deficits do not resemble typical dementia(9). This may suggest that long COVID hinders the prediction and decision rather than the memory process.

Sigma-1 receptors regulate intracellular proteostasis, calcium homeostasis, and especially, the dynamic energy balance in the brain(10). Through sigma-1 receptor chaperone activity, the sigma-1-receptor agonist may attenuate endoplasmic reticulum stress in cells, resulting in a blockade against inflammatory events. The sigma-1 receptors also affect dopamine neurotransmission(11). Taken together, the mechanism may shift energy utilization and prediction coding. Some selective serotonin reuptake inhibitors, including fluvoxamine, sertraline, fluoxetine, and
citalopram, have high to moderate affinities for sigma-1 receptors and show promising therapeutic effects in postCOVID depression(12). The dysautonomia symptoms such as fatigue and slow cognition highlight energy regulation as a key element in the psychopathology of the patient in the present case. The diminished HRV changes with circadian rhythms may reflect problems with energy regulation. Evaluating the effects of sertraline may be difficult due to the use of other medications for mood stabilization. However, based on the patient's response to sertraline within 2–3 weeks, we believe it played a significant role in her recovery. However, this hypothesis requires further confirmation. We plan to carefully simplify her medications and may try a regimen containing only sertraline to elucidate the clinical relevance of this medication.

The concept of allostasis has led us to reframe the unpredictable and heterogeneous neuropsychiatric symptoms associated with COVID-19 as consequences of energy dysregulation. To validate this hypothesis, future research involving direct observations and experimental manipulation is needed.