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Case Report

Emergence of first manic episode in recovered COVID-19 patients: A case series from Egypt

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ABSTRACT

Background: In December 2019, the novel coronavirus (COVID-19) infection was first reported in Wuhan city, China, which had rapidly spread as a global pandemic. This infection was commonly presented by respiratory and /or gastrointestinal symptoms. However, it is still unclear whether COVID-19 infection could be associated with central nervous system (CNS) damage which would result in the development of neuropsychiatric symptoms. **Case series:** The authors described five cases of suddenly emerged manic episodes during the pandemic of COVID-19. They all had positive findings of ribonucleic acid (RNA) tests for COVID-19 in specimens of sputum. The patients developed manic symptoms during the recovery period of their illness. We presented the symptoms and described the diagnosis, clinical course, and treatment of each case. **Limitation:** The limited number of cases would limit the generalizability of the association. Moreover, the CSF PCR testing for the COVID-19 virus was not conducted simultaneously when a positive throat swap was recorded. **Conclusion:** The case series of newly emerged manic symptoms associated with COVID-19 infection highlights the essential need for evaluation of mental health status and would contribute to our understanding of the potential risk of CNS affection by COVID-19 infection.

Introduction

Since December 2019, the world's attention was attracted to Wuhan city, the capital of Hubei Province, China, due to an outbreak of the COVID-19 virus infection. There were rapidly increasing numbers of established cases caused by human-to-human transmission, with a tremendous rise in deaths not only in China but also worldwide. In January 2020, the World Health Organization (WHO) declared that the COVID-19 outbreak was a public health emergency of global concern (World Health Organization, 2020). The clinical manifestations of patients with COVID-19 infection varied from asymptomatic to acute flu-like symptoms such as cough, fever, and shortness of breath, which might progress to respiratory distress and even failure, exhaustion, as well as gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Moreover, cardiac and other organ dysfunctions and superimposed infections were also reported (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020).

Various studies had documented the deleterious impact of COVID-19 virus infection on the mental well-being and quality of life in various populations including COVID-19 patients (Abdelghani, Hassan, Alsadik, Abdelmoaty, Said, & Atwa, 2021), physicians (Abdelghani, Hassan, Elgohary & Fouad, 2021) and other healthcare

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providers (Abdelghani, Mahdy, & El-Gohari, 2021), patients with pre-existing chronic diseases (Abdelghani, Hamed, Said, & Fouad, 2021), and even the general population (Aljemaiah et al., 2021). In addition, few studies had documented the association between COVID-19 infection and neuropsychiatric symptoms such as brief psychosis, paranoid symptoms, and delirium (Ferrando et al., 2020; He et al., 2021; Smith et al., 2020). However, the pathogenesis of these sequelae was still unclear. The etiology was postulated to be attributed to various factors including brain infection, cerebrovascular hyper-coagulopathy, stress-inducing problems such as treatment interventions, emotional disturbances, unemployment, social isolation, COVID-19-related stigma, or drug-induced (corticosteroids or antiviral medications) (Richardson et al., 2020; Zhou et al., 2020).

Few data were reported about manic episodes which emerged during recovery from COVID-19 infection without previous history or family history of mood disorders. The clinical implication of that work is to encourage prospective studies that are essential to determine the real effect and correlates of COVID-19 infection on precipitating manic symptoms and other mood disorders and to furtherly investigate the psychopathology of COVID-19 infection.

Case presentation

First case

On July 20, 2020, a 57-year-old male patient was brought to the psychiatric outpatient clinic at Zagazig University with symptoms of mood elation, hyperactivity, psychomotor agitation, pressured speech, decreased need to sleep (only 2 to 3 hours per night was enough), increased appetite, increased self-esteem, increased pleasurable (sexual) activity and delusion of persecution (claiming that the neighbors wanted to harm him). The patient had no previous or family history of primary mood or psychotic disorders. The patient was a nonsmoker, known asthmatic stabilized on bronchodilators, and denied any history of substance use disorders.

Ten days before the emergence of manic symptoms, the patient reported an inability to smell and taste, rhinorrhea, a fever of 38.8, weight cough, and fatigue. His oxygen saturation was 94%, and his respiratory rate was 16. His chest CT scan showed multiple bilateral consolidations and ground glass patches. Later, the diagnosis of COVID-19 was confirmed by a positive throat swab. The laboratory findings revealed serum ferritin 420.8, D-dimer 0.42, ESR (first hour) 24 negative CRP, normal CBC, normal PT and PTT, normal kidney and liver function except for slightly elevated AST and ALT, and normal abdominal ultrasonography except for mildly enlarged liver displaying slightly coarse echo pattern. The following drugs were prescribed for the patient under the supervision of his chest physician: Paracetamol 500 every 8 hours, bromhexine 5 ml every 8 hours, clarithromycin, 500 mg twice daily, theophylline 150 mg twice daily and betamethasone one ampule once. Within one week, previous symptoms started to disappear. 3-days later, his family noticed the emergence of the previously reported mood and behavioral changes. Treatment included olanzapine 15 mg at night. After 3 weeks of treatment, the patient showed gradual and marked responses, especially mood, sleep, and speech symptoms, and was advised to continue the prescribed drug.

Second case

On July 24, 2020, 69 years old female patient came with her family to the outpatient clinic at Zagazig University and presented with symptoms of being talkative, irritable, energetic, and verbally aggressive. The family reported insomnia and early waking, increased appetite especially for pastries, increased pleasurable activity (wearing and buying gold pieces) delusion of persecution (claimed that others tried to hurt her).

The previous symptoms developed two weeks after the patient's complaints of nausea and vomiting, dry cough, fever of 38.9, headache, and fatigue. She sought medical treatment at the isolation hospital in her region for 7 days and continued her protocol of treatment at home. The diagnosis of COVID-19 infection was confirmed by a positive throat swap. The advised protocol prescribed for her was Paracetamol 1000 mg every 8 hours, Ceftriaxone 1000 mg ampule for 5 days, Azithromycin 500 mg once daily for 6 days, Levodropropizine 5ml every 8 hours, Ivermectin 6 mg 4 tablets once repeated after 3 days, Enoxaparin sodium 4000 IU, Lactoferrin 100 mg sachet twice daily, and Vitamin C 500 mg capsule twice daily. The patient improved within 1 week of treatment. The laboratory finding during the time of

admission revealed high blood sugar of 610 mg/dl (discovered for the first time). Other investigations showed moderate leukocytosis at 17.81 and neutrophilia at 92.5. Her CT brain showed nonspecific age-related brain atrophy. The patient had no history of medical illness except for hypertension 8 years ago controlled on amlodipine 5 mg, hydrochlorothiazide 12.5 mg, and Olmesartan 20 mg. She has no psychiatric history or family history of any mental illness or substance abuse.

When she came to the psychiatric clinic, we prescribed risperidone 2 mg which was gradually increased to 4 mg at night. She started to improve after 4 days of the last dose and completely recovered within 2 weeks of treatment. Psychiatric follow-up during the following weeks was reassuring. The patient showed a stabilized mood and became calm with normal sleep, speech, and appetite continuing the same prescribed drug.

Third case

On June 4, 2021, a 35-year-old female patient came with her husband to the emergency room in a general hospital after the death of her father with COVID-19. She claimed symptoms of depressed mood, insomnia, and tingling in both hands. A general practitioner prescribed her midazolam 5 mg ampoule STAT, and she was discharged as she became somewhat quiet. Two days later, she gradually became talkative, weeping most of the time, then her mood was switched to irritable and in a loud voice refusing anyone to interrupt her. Later, the husband noticed her decreased sleep hours with early awakening and hyperactivity, as well as engagement in unnecessary pleasurable activities (excessive shopping). She accused her mother-in-law that she was making black magic for her husband and that neighbors were spying on her social media accounts. One week later, her husband took her to the same hospital where the GP gave her another midazolam 5 mg amp and consulted a psychiatrist who prescribed Haloperidol 5 mg IM twice daily, Biperiden 2 mg twice daily, and Olanzapine 10 mg at night. She became quiet and sedated with good vital signs. The patient had no history of chronic medical illness, primary mood or psychotic disorders, or substance use disorders.

Her husband informed her that three weeks before the former symptoms, the patient complained of flu-like symptoms, cough, fever, generalized body ache, headache, and fatigue. These symptoms started 2 days after she visited her deceased father who was infected with the coronavirus. She sought medical treatment with a pulmonologist who requested CT chest revealing multiple pneumonic patches. Her labs revealed elevated CRP and serum ferritin, and Oxygen saturation was 88. The diagnosis of COVID-19 infection was confirmed by a positive throat swap. Medications given included Ceftriaxone 1 gm ampoule once daily, dexamethasone ampoule twice daily for 5 days, and linezolid 600 mg daily for 5 days. She continued her protocol of treatment at home and started to improve one week after treatment onset.

Fourth case

On June 13, 2021, a 34-year-old female patient came with her mother to a psychiatric clinic suffering from an insidious course of symptoms of irritable mood, insomnia, hyperactivity and talkativeness, and psychomotor agitation. Later, she started screaming and shouting, insulting her family members with obscene words, spitting on them, and producing sounds like goats. On their way to the clinic, her family forcibly prevented her from standing in front of a running car. The patient had no history of chronic medical illness, primary mood or psychotic disorders, or substance use disorders. After the psychiatric interview, the patient had prescribed olanzapine 20 mg once daily at night, sodium valproate 500 mg three times daily, haloperidol 5 mg IM twice daily, and biperiden 2 mg twice daily.

Four weeks before the symptoms, the patient complained of cough, fever, generalized body ache, and fatigue. She sought medical treatment with a pulmonologist who requested CT chest showing mild pneumonic patches, and labs revealing elevated CRP and serum ferritin, and lymphopenia. The diagnosis of COVID-19 infection was confirmed later by a positive throat swap. She received linezolid 600 mg daily for 5 days, four tablets of Ivermectin 6 mg once daily for 4 consecutive days, and paracetamol 500 mg 4 times daily with home isolation. The patient's condition started to improve after 5 days of treatment. After three weeks of recovery from Covid-19 symptoms, she started to gradually develop psychiatric symptoms.

Fifth case

On May 24, 2021, a 47-year-old male patient came alone to a psychiatrist complaining of symptoms of depressed mood, lack of interest, chest tightness, unexplained weeping, lack of concentration, fatigue, and suicidal thoughts which developed over two weeks. Later, the patient neglected his work and became socially withdrawn. CT brain was performed, which looked normal. The depressive symptoms persisted for the next four months despite prescribing venlafaxine 75 mg for one month and then 150 mg for 3 months. After revising the patient's psychiatric condition, it was documented that the patient was diagnosed one year earlier with bipolar disorder, manic episodes by another psychiatrist when he had symptoms of elated mood, insomnia, talkativeness, hyperactivity, spending a lot of money on non-useful goods and grandiosity thoughts. The prescribed medications were olanzapine 10 mg once daily at night and sodium valproate 1000 mg twice daily. Manic symptoms disappeared gradually after one month of psychotropic medications. Therefore, this patient was eventually diagnosed with bipolar I disorder, recurrent, current episode depressive, and prescribed Olanzapine/Fluoxetine combination 6/25 mg once daily at night.

However, the patient's family reported that the manic symptoms developed three weeks after symptoms of sore throat, mild cough, and anosmia. He sought medical treatment with an internist who requested CT chest showing mild pneumonic patches, and labs revealing elevated CRP and serum ferritin, and leukopenia. The diagnosis of COVID-19 infection was confirmed later by a positive throat swap. The prescribed medications included doxycycline 200 mg on the first day of the course, followed by a maintenance dose of 100 mg regularly for 7-10 days, three tablets of Ivermectin 6 mg once daily for 4 consecutive days and paracetamol 500 mg 4 times daily, with home isolation. The patient improved within 7 days of treatment and stopped his treatment.

Discussion

In this study, we reported five cases presented with manic episodes shortly after recovery from infection with SARS-CoV-2. These cases had no history of primary mood or psychotic disorders, or substance use disorders. It was reported that depression and anxiety were the most commonly detected psychiatric symptoms in patients infected with SARS-CoV-2, and this was logic, mostly due to fear of infection and the socio-cultural burden associated with COVID-19 infection. A meta-analysis of twelve large studies reported that the pooled prevalence of depression in the general population during the COVID-19 outbreak is 25% (Bueno-Notivol et al., 2021). Other studies reported that the prevalence of anxiety during the COVID-19 period ranged from 18% to 45% (Mazza et al., 2020; Özdin & Bayrak Özdin, 2020). The explanation suggested in most of these studies was that excessive exposure to social media news would be associated with higher levels of anxiety and depression (Gao et al., 2020; Ni et al., 2020). Social media would lead to a false fear reaction (''fake news'') during the spread of the disease, rather than real risk (Sommariva et al., 2018). In addition, socioeconomic factors such as unemployment (Mazza et al., 2020), economic burden (Lei et al., 2020), and lack of social support (Ni et al., 2020) might also be considered contributing factors to the higher rates of emotional instability.

However, the condition is different when speaking about the development of manic symptoms. It would be rare to report cases of bipolar I disorder or acute psychosis in patients with COVID-19 infection without a past or family history of a psychiatric illness, as these disorders have a strong biological base. To our knowledge, there was only one single case report for a SARS-CoV-2-infected patient who presented with manic-like symptoms (Lu et al., 2020). Surprisingly, we reported a total of five cases of typical manic episodes in patients recently recovered from COVID-19 infection without past or family history of primary mood or psychotic disorders, or substance use disorders, which would be considered one of the very few reports about manic symptoms in patients infected with SARS-CoV-2.

The explanation of the development of concurrent manic symptoms would be related to biological changes that occurred in the brain of SARS-CoV-2 infected patients referring to the ferocious nature of this infection. This would happen owing to the direct effect of the virus on the CNS. In line with this potential, a case of meningitis/encephalitis in a SARS-CoV-2-infected patient was reported (Moriguchi et al., 2020). Besides, these brain

changes would be attributed to the virus-induced neuroinflammation with the production of high amounts of pro-inflammatory mediators including chemokines in the affected patients, with activation of T-helper-1 (Th1) cell responses (Huang et al., 2020). Previous studies found that inflammation-associated immune activation with the release of inflammatory factors was postulated as one of the mechanisms that could lead to the pathogenesis of bipolar disorder (Mazza et al., 2019; Réus et al., 2015).

In conclusion, this case series of COVID-19 patients with newly emerged manic episodes highlighted the high possibility of an association between COVID-19 infection and a wide array of psychiatric illnesses and raised the importance of thorough and accurate evaluation of mental health status in those patients for early discovery and management of any mental illness in those patients.

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