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Research paper

First report of manic-like symptoms in a COVID-19 patient with no previous history of a psychiatric disorder

Shaojia Lu[a,1], Ning Wei[a,1], Jiajun Jiang[a], Lingling Wu[a], Jifang Sheng[b], Jianying Zhou[c], Qiang Fang[d], Yu Chen[e], Shufa Zheng[e], Feng Chen[f], Tingbo Liang[g,*], Shaohua Hu[a,*]

[a] Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine, Key Laboratory of Mental Disorder's Management of Zhejiang Province, Zhejiang Engineering Center for Mathematical Mental Health, Hangzhou, Zhejiang, China
[b] Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[c] Department of Respiratory, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[d] Department of Intensive Care Unit, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[e] Department of Clinical Laboratory, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[f] Department of Radiology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China
[g] Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang Provincial Key Laboratory of Pancreatic Disease, Hangzhou, Zhejiang, China

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ABSTRACT

Background: In December 2019, the novel coronavirus (SARS-CoV-2) infection was first reported in Wuhan city, central China, which has spread rapidly. The common clinical features of patients with SARS-CoV-2 infection included fever, fatigue, and damage to the respiratory or digestive system. However, it is still unclear whether SARS-CoV-2 infection could cause damage to the central nervous system (CNS) inducing psychiatric symptoms.
Case report: Herein, we present the first case of SARS-CoV-2 infection with manic-like symptoms and describe the diagnosis, clinical course, and treatment of the case, focusing on the identifications of SARS-CoV-2 in the specimen of cerebrospinal fluid (CSF). The patient developed manic-like symptoms when his vital signs recovered on illness day 17. After manic-like attack, the detection of SARS-CoV-2 specific IgG antibody in CSF was positive, while the reverse transcriptase-polymerase chain reaction (RT-PCR) on CSF for the SARS-CoV-2 was negative. The patient received Olanzapine for treatment and his mood problems concurrently improved as indicated by scores of Young Manic Rating Scale (YMRS).
Limitation: This is a single case report only, and the RT-PCR test for SARS-CoV-2 in CSF was not performed simultaneously when SARS-CoV-2 was positive in samples of sputum and stool.
Conclusion: This first case of COVID-19 patient with manic-like symptoms highlights the importance of evaluation of mental health status and may contribute to our understanding of potential risk of CNS impairments by SARS-CoV-2 infection.

1. Introduction

Since December 2019, Wuhan, the capital city of Hubei Province, China, has attracted the global attention due to an outbreak of SARS-CoV-2 infected pneumonia (COVID-19). As a result of the people-to-people transmission of SARS-CoV-2, there are rapidly increasing numbers of confirmed cases and deaths not only in China, but also throughout the world. The World Health Organization (WHO) has declared on January 30 that the SARS-CoV-2 outbreak is a public health emergency of international concern (PHEIC) (World Health Organization, 2020).

The identified clinical features of patients with SARS-CoV-2 infection mainly included fever, fatigue, and disturbances of the respiratory and digestive system, such as cough, sputum production, shortness of breath, anorexia, and diarrhea (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020). It is still unclear whether SARS-CoV-2 infection could cause damage to the central nervous system (CNS) inducing psychiatric symptoms.

This first case report aimed to raise an awareness of the potential virulence of SARS-CoV-2 on CNS inducing psychiatric symptoms. We

* Corresponding authors.
E-mail addresses: liangtingbo@zju.edu.cn (T. Liang), dorhushaohua@zju.edu.cn (S. Hu).
[1] These authors contributed equally to this work.

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also discussed possible pathophysiological pathways that might explain the link between SARS-CoV-2 infection and the manic-like symptoms presented by this patient.

2. Case report

On January 29, 2020, a 51-year-old male patient was admitted to The First Affiliated Hospital, Zhejiang University School of Medicine with a chief complaint of fever and pharyngalgia for 4 days, and chest distress, and shortness of breath for 1 day. The patient was a healthy non-smoker without a past or family history of mental disorders. On admission, the physical examination revealed a body temperature of 37.3 ˚C, blood pressure of 117/72 mmHg, pulse of 66 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 92% while the patient was breathing ambient air. Chest computed tomographic (CT) scan showed bilateral patchy shadows and ground glass opacity in the lung. The diagnosis of COVID-19 was confirmed by positive findings of ribonucleic acid (RNA) tests for SARS-CoV-2 in specimens of sputum and stool from the patient.

After admission, the routine laboratory tests were performed and re-examined as needed, especially including identifications of SARS-CoV-2 RNA in specimens of sputum and stool, blood routine exam, plasma levels of Interleukin (IL)-6, IL-10, and C-reactive protein (CRP). The patient received Arbidol Tablets, Moxifloxacin, Darunavir and Cobicistat Tablets, and Methylprednisolone along with supportive care for treatment. The laboratory tests detected leukopenia, increased plasma levels of IL-6, IL-10, and CRP in the acute phase of the illness in our patient. During this time, the RNA tests for SARS-CoV-2 in specimens of sputum and stool were positive. The patient's clinical condition improved from illness day 11 (hospital day 7) and recovered on illness day 16 (hospital day 12). In the meantime, the routine laboratory tests returned to nearly normal and the RNA tests for SARS-CoV-2 in samples of sputum and stool were negative. Thus, the antiviral therapy was discontinued orderly and the dose of Methylprednisolone tablets was gradually reduced.

On illness day 17 (hospital day 13), the patient appeared to be excited, talkative, irritable, and energetic. The patient said that he was the emperor who could end the current epidemic situation, and his great achievements would be recorded in history. He began to wake up early, and then speak loudly. His consciousness was clear and orientation was correct. A manic-like attack was considered, lumbar puncture performed on illness day 20 showed an opening pressure of 165 mmH_2O, with free flow of CSF. Total CSF protein was 0.30 g/L. Microscopy showed a leukocyte count of 10 per μl. The test for SARS-CoV-2 RNA in CSF was negative. However, the detection of SARS-CoV-2 specific IgG antibody in CSF was positive (CSF sample received on illness day 20 and tested on illness day 24). The brain MRI showed small ischemic lesions located at basal ganglia and semiovale center (**Fig. 1**), suggesting no major pathological changes in the brain.

After manic-like attack, the patient received intramuscular injection of 5~2.5 mg haloperidol twice a day on the first 2 days of manic-like attack, combining with Olanzapine which was gradually titrated to 10 mg per day. The Young Manic Rating Scale (YMRS) (Young et al., 1978) was introduced to evaluate emotional status every day. The patient's score of YMRS was decreasing gradually when antipsychotics were added. His YMRS score decreased from 36 on the 1st day to 2 on the 9th day of manic-like attack.

Symptoms and laboratorial tests according to illness days and hospital days, from January 23 to February 20, 2020, were shown in **Fig. 2**. This study obtained approval from the Institute Ethical Committee of The First Affiliated Hospital, Zhejiang University School of Medicine (ITT20200041A). An informed consent for publication of the case details was provided by our patient.

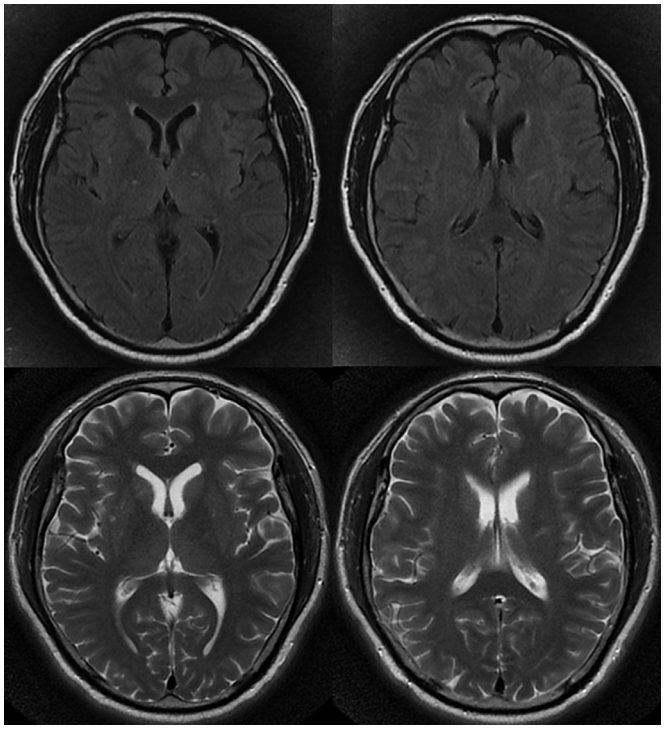

Fig. 1. Brain magnetic resonance imaging showing small ischemic lesions located at basal ganglia and semiovale center on February 13, 2020 (Hospital day 16, Illness Day 20).

3. Discussion

In this study, we firstly reported a case of SARS-CoV-2 infected patient with manic-like symptoms. As far as we know, it was the first time that SARS-CoV-2 was tried to be identified and its specific IgG antibody was detected from a specimen of CSF in a COVID-19 patient with manic-like symptoms. The SARS-CoV-2 is a positive-strand RNA virus that causes severe respiratory syndrome in humans. The genetic sequence of SARS-CoV-2 shares 79.5% similarity with that of SARS-CoV and is about 96% identical to the bat coronavirus BatCoV RaTG13 (Zhou et al., 2020).

A previous case reported that Chikungunya virus (CHIKV) infection might act as a trigger for manic episode in a bipolar patient, however, the underlying mechanisms remain poorly investigated (Figueiredo et al., 2018). One explanation could be the direct effect of virus in CNS. Recently, the first case of meningitis/encephalitis associated with SARS-CoV-2 was reported and the specific SARS-CoV-2 RNA was detected in CSF in a 24-year-old patient with COVID-19 (Moriguchi et al., 2020). This case highlighted the neuroinvasive potential of SARS-CoV-2 inducing CNS symptoms. In our patient, the detection of SARS-CoV-2 specific IgG in CSF was positive which could be treated as evidence of a past CNS infection by SARS-CoV-2, in this context, we suspected that manic episode might be a delayed response to CNS infection by SARS-CoV-2. However, the RNA test in CSF was negative and the current result did not support our speculation directly. Despite that, due to the multiple influent factors on RNA test and possibility of a false-negative test result since the CSF test was not performed simultaneously when SARS-CoV-2 was positive in samples of sputum, the present intriguing hypothesis should be investigated further in future.

Another interpretation of the link between SARS-CoV-2 infection and manic-like symptoms in our patient could be the effect of inflammation. Previous findings have demonstrated that infection-associated immune activation and subsequent release of inflammatory factors was one of the potential pathogenesis of bipolar disorder (BD)

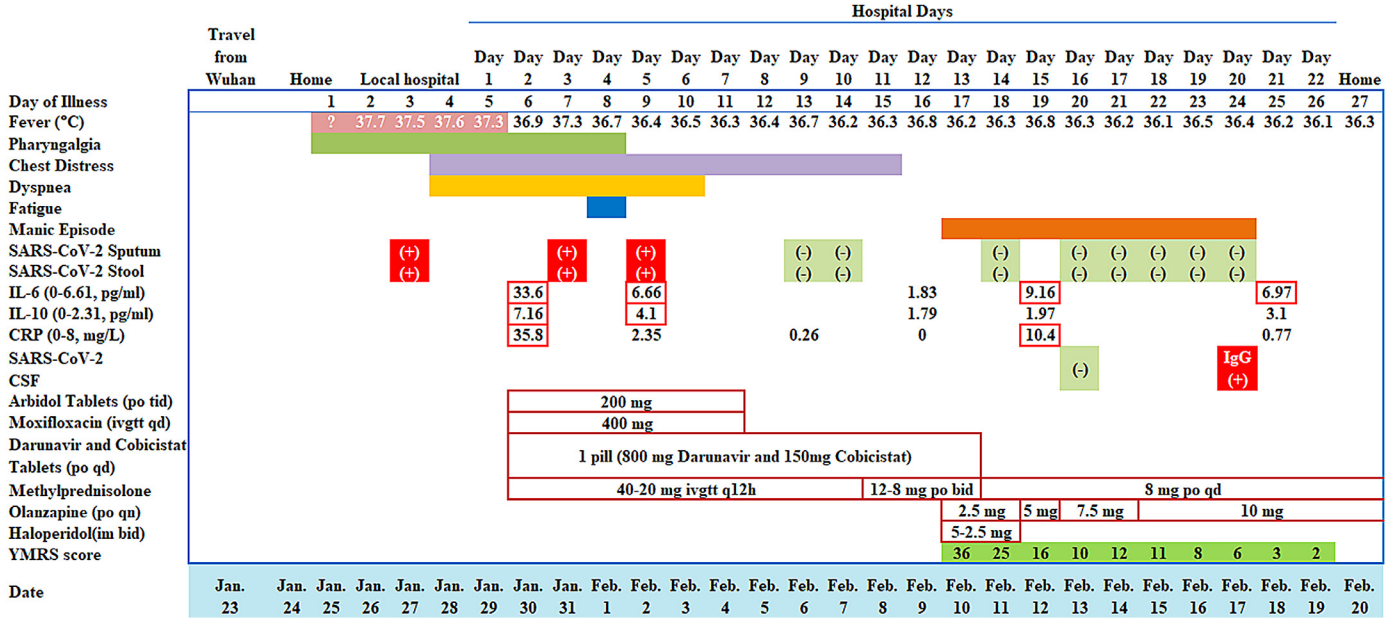

Fig. 2. The whole illness course according to illness days and hospital days, January 23 to February 20, 2020.

(Benros et al., 2013; Reus et al., 2015). Interestingly, a recent study further indicated that inflammatory changes occurred especially during acute episodes of mania in BD patients (Mazza et al., 2019). It was found that patients infected with SARS-CoV-2 produced high amounts of pro-inflammatory factors and chemokines, probably leading to activated T-helper-1 (Th1) cell responses (Huang et al., 2020). The present study also detected increased plasma levels of IL-6, IL-10, and CRP in the acute phase of the illness in our patient, in this context, we further hypothesized that SARS-CoV-2 infection could initiate a cascade of inflammation that might contribute to manic-like symptoms.

Moxifloxacin, an antibiotic belonging to quinolones, was used in this patient. As we know, the most commonly reported psychiatric adverse events caused by quinolones is mania (Tome and Filipe, 2011). Although the dose-effect and time-effect relationships of this adverse drug reaction (ADR) had not been elucidated distinctly, we thought that the manic-like symptoms of our patient might be not triggered by Moxifloxacin which had been withdrawn for 6 days. Additionally, as reported, the most frequent ADRs after short-term corticosteroid use included euphoria and hypomania (Drozdowicz and Bostwick, 2014). Previous findings observed that corticosteroids therapy had 4-to-5 fold higher risk of developing mania, following a dose-response correlation, increased with the magnitude of the initial daily dose (Fardet et al., 2012). But for the present case, the use of Methylprednisolone tablets was reducing to a very low dose, which was also less likely to trigger mania.

4. Limitation

The present study has certain limitations. First, this is a single-case report, the assumptions raised must be confirmed with future studies. Second, the manic-like symptoms were not able to be predicted in the acute period of illness in our patient. In that case, the limitation of the present study was that the RT-PCR test for SARS-CoV-2 in CSF was not performed simultaneously when SARS-CoV-2 was positive in samples of sputum and stool, which might result in a probability of false-negative outcome. Furthermore, the positive finding of SRAS-CoV-2 specific IgG in CSF elevated this possibility.

In conclusion, this first case of COVID-19 patient with manic-like symptoms highlights the importance of evaluation of mental health status and may contribute to our understanding of potential risk of CNS impairments by SARS-CoV-2 infection.

Contributors

Author Shaojia Lu designed the study and wrote the first draft of the manuscript. Author Ning Wei collected the clinical data and performed the statistics. Authors Jiajun Jiang and Lingling Wu reviewed the literature. Authors Jifang Sheng, Jianying Zhou, and Qiang Fang guided the treatment strategy. Authors Yu Chen, Shufa Zheng, and Feng Chen performed the laboratory tests and radioscopy. Authors Shaohua Hu and Tingbo Liang also designed the study and had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to and have approved the final manuscript.

Role of the funding source

None.

Declaration of Competing Interest

None.

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