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Restlessness with manic episodes induced by right-sided multiple strokes after COVID-19 infection: A case report

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Abstract:

Ischemic stroke is a major complication of coronavirus infection 2019 (COVID-19). During the COVID-19 pandemic, multiple strokes occurred in many elderly people. Among them, poststroke mood disorders such as depression are relatively common. However, restlessness with manic episodes has rarely been reported. We experienced an elderly patient who became manic shortly after recovering from COVID-19 infection, which turned out to be right-sided multiple strokes. The manic state improved as the strokes stabilized, suggesting that impaired blood flow was the cause of the manic symptoms. Primary mania increases blood flow in the left hemisphere, whereas right-sided strokes may relatively increase blood flow in the left hemisphere, which may have induced manic symptoms in this case. Multiple right-sided strokes after COVID-19 infection can cause mania, and the mechanism of poststroke mania needs to be investigated in the future.

Keywords:

COVID-19, manic episode, multiple strokes, right-left imbalance of blood flow

Introduction

Ischemic stroke is a major complication of coronavirus infection 2019 (COVID-19). During the COVID-19 pandemic, multiple strokes occurred in many elderly people.[1] Among them, mood disorders following stroke such as depression are relatively common. However, mania has been reported as an uncommon symptom after cerebrovascular accident and occurs much less frequently than depression or other mood disorders after cerebrovascular accident, accounting for <1% of cases.[2] After a stroke, patients may present with manic episodes of abnormally elevated arousal, emotion, and energy levels, which may be related to changes in blood flow due to the stroke.[3] We experienced an elderly patient who suddenly developed mania after healing from COVID-19 infection, which turned out to be right-sided multiple strokes. We discussed this case from two points of view: the relationship between COVID-19 infection and multiple strokes, and the mechanism of mania caused by multiple strokes.

Case Report

An 84-year-old right-handed man was admitted to our hospital through emergency transport service from a nursing home due to mental confusion, agitation, and appetite loss. He was previously healthy but was infected with COVID-19 a month ago and recovered in 1 week without complications. This patient was infected during the seventh wave of the COVID-19 pandemic in Japan, when more than 200,000 people/day were infected with the Omicron variant at its peak. During this period, some elderly people infected with the Omicron variant developed multiple cerebral infarctions.[4] However, 2 weeks before presentation, he suddenly developed psychotic confusion

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including inappropriate speech and agitation, and was taken to the psychiatry department of a general hospital, where he was diagnosed with psychomotor agitation associated with mania and started on 2 mg risperidone. However, since his symptoms did not improve and he also suffered from anorexia, he was transferred to our hospital.

On admission, he showed partially impaired orientation to time but had well-preserved orientation to place and person. Neurological examination revealed no obvious motor or sensory deficits. He appeared agitated, and was talkative with an elated, euphoric mood. Mild dysarthria appeared along with persistence of restlessness and manic features. Blood tests showed a high D-dimer level of 5.6 μg/mL but otherwise a mildly elevated white blood cell count and mildly elevated urea nitrogen, suggesting dehydration due to psychomotor excitement. An electrocardiogram showed no atrial fibrillation or other arrhythmias. Possible differentials for mania included primary mania, mixed mood disorder, frontotemporal dementia, hyperthyroidism, systemic lupus erythematosus, Huntington's disease, Cushing's syndrome, and drug-related conditions such as steroid medications, but the patient had no psychiatric symptoms before onset, the patient was elderly at onset, and blood test data did not raise suspicion of these diseases. Therefore, considering the possibility that the patient presented a manic state as a psychiatric symptom due to an organic brain disorder, brain magnetic resonance imaging (MRI) was performed. Diffusion-weighted images (DWIs) showed multiple hyperintense lesions in the right frontal and right parietal lobes [Figure 1]. Fluid-attenuated inversion recovery images also showed pale hyperintense areas consistent with the hyperintense areas on DWI, indicating multiple subacute cerebral infarcts in the region of the right middle cerebral artery [Figure 2]. Magnetic resonance angiography showed no stenosis in the cervical artery, and almost all main arteries were depicted, but the peripheral signal of the right middle cerebral artery was reduced, indicating that blood flow in the right middle cerebral artery region is reduced [Figure 3]. Risperidone was discontinued due to decreased food intake and dysphagia, and ramelteon 8 mg and suvorexant 15 mg were administered for insomnia. Intravenous fluids were administered to compensate for fluid deprivation due to agitation and decreased oral fluid intake. For cerebral infarction, 30 mg/day of edaravone was administered for 2 weeks. After that, aspirin 75 mg/day and edoxaban 15 mg as a direct oral anticoagulant were started for stroke prevention. Restlessness and mania resolved spontaneously within a month without administration of antimanic or antipsychotic drugs. Consent for the presentation of the case was obtained from the patient and family.

Discussion

This is a rare case of multiple strokes with manic symptoms after COVID-19 infection. COVID-19 infection increases the risk of thrombotic disease, and there are increasing reports of rare cerebral infarctions in the elderly, including severe bilateral infarctions and foreign accent syndrome with left insular infarction.[1,5] Ischemic stroke is a major complication of COVID-19 infection.[6] In a multivariate analysis controlling for race/ethnicity, COVID-19 infection was significantly and independently associated with large-vessel occlusive stroke, with an odds ratio of 2.4.[7] The mechanism by which COVID-19 induces cerebral infarction is not fully understood. SARS-CoV-2 is internalized into cells by binding of the viral spike glycoprotein to angiotensin-converting enzyme 2 (ACE2) on the cell membrane, and ACE2 is also expressed in brain tissue. As a result, inflammation, oxidative stress, and thrombotic responses may have been induced in the brain.[8] COVID-19-related stroke is characterized by hypercoagulability and hyperinflammation that may favor strokes through microvascular circulation abnormalities, microthrombus formation, and multifocal lesions.[1] Endothelial damage, hypercoagulability, viral myocarditis, and hypoxic

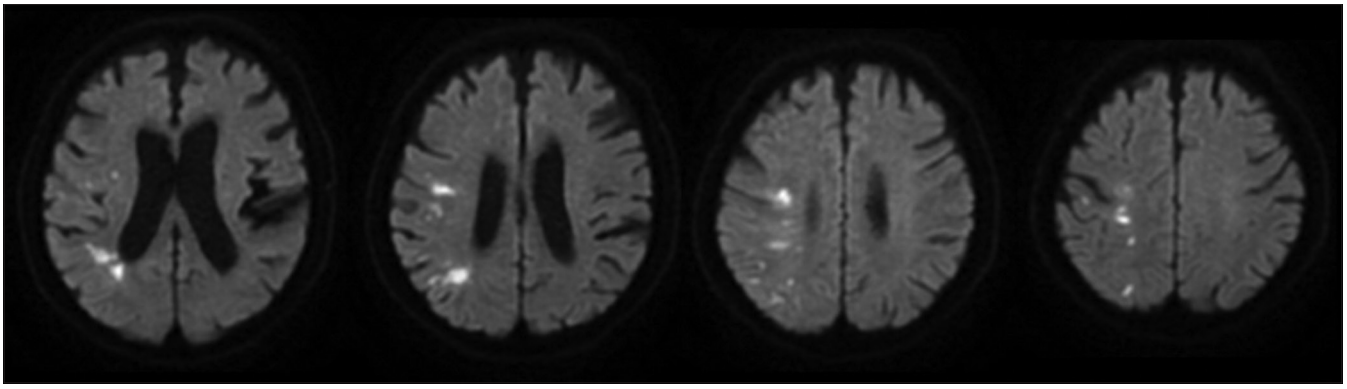

Figure 1: Diffusion-weighted images of the patient. Multiple hyperintense lesions were found in the right frontal and right parietal lobes, indicating the presence of relatively acute multiple strokes

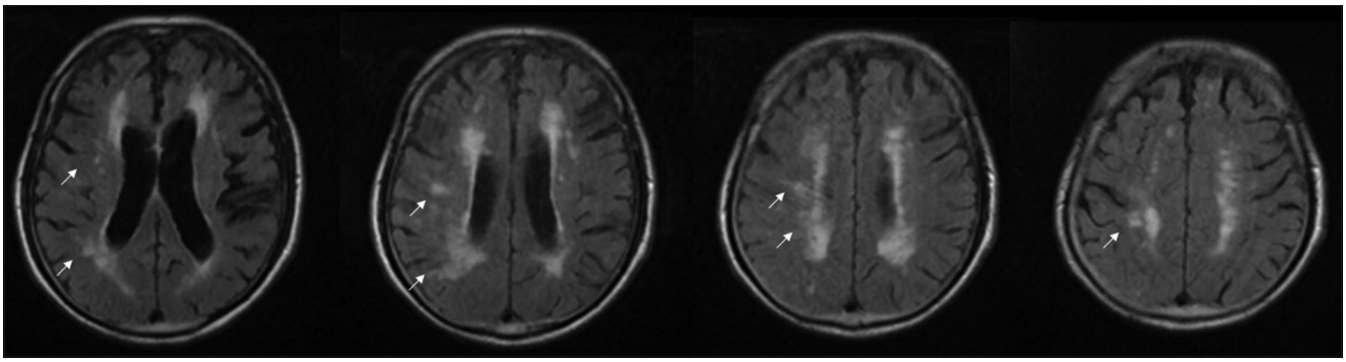

Figure 2: Fluid-attenuated inversion recovery images. A pale hyperintense lesion appeared in the area that showed hyperintense signal on DWI and was considered to be multiple subacute strokes (indicated by white arrows). DWI: Diffusion-weighted image

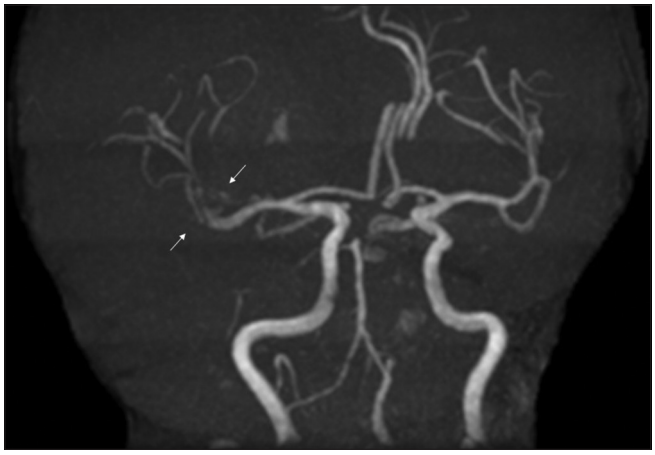

Figure 3: Magnetic resonance angiography. There was a clear left-right difference with decreased vascular delineation in the right middle cerebral artery region (indicated by white arrows)

damage have been proposed as the pathogenesis of COVID-19-related strokes,[9] and in this case, there was an unexplained high D-dimer level after COVID-19 infection, so hypercoagulability was one of the causes of the multiple strokes. Omicron variant has milder respiratory symptoms, but stroke complications still need to be considered.

Mood disorders associated with acute cerebral infarction are relatively common, such as depression, but restlessness with mania is rare, making it difficult to diagnose cerebral infarction from manic symptoms. Poststroke mania is rare, accounting for <1% of poststroke mood disorders. The majority of patients present with elevated mood as the first symptom. Other frequent symptoms are increased rate and volume of speech, insomnia, and agitation. Gender differences are reported more frequently in males, but the age of onset is higher than expected for primary mania. The location of stroke was mostly in the right hemisphere.[10] In the present case, the patient visited a general hospital with both stroke center and psychiatry department at the onset of manic symptoms, but the presence of cerebral infarction was not noticed, probably because the patient had predominantly psychiatric symptoms without clear motor impairment. Lesions that cause mania after stroke may be located mostly in the right hemisphere, as in this case. The single-photon emission computed tomography (SPECT) of a patient with manic symptoms after right parietal lobe stroke showed not only decreased blood flow around the right-sided infarct site but also increased activity in the left inferior frontal lobe and anterior insula, suggesting that functional changes in the contralateral hemisphere of the infarcted brain may induce manic symptoms.[11] Primary mania shows an unbalanced pattern of regional cerebral blood flow in the inferior frontal cortex that is greater on the left, and manic symptoms are associated with relatively increased activity in the left prefrontal cortex.[12] Recent functional MRI (fMRI) studies have observed altered functional connectivity of the orbitofrontal cortex and left ventral striatum in patients with bipolar disorder.[13] In a study comparing cerebral blood flow in manic and normal individuals by voxel-wise regression, mania was associated with greater cerebral blood flow in the left posterior occipital lobe cortex and superior segment, while right posterior occipital lobe, angular gyrus, and middle temporal gyrus were associated with smaller cerebral blood flow, indicating a left-right difference. Greater cerebral blood flow in the left temporal occipital lobe cortex was correlated with lower mental symptoms and work speed.[14] The present case is based on the impairment of various brain regions on the right, for which altered functional connectivity may have caused the manic symptoms. Considering the above and the results of SPECT and fMRI studies to date, multiple right cerebral infarcts may have altered the distribution of blood flow in the left and right cerebral hemispheres, resulting in hyperfunction of the left hemisphere, similar to the blood flow pattern of primary mania. Once the cerebral infarction stabilized, the imbalance in blood flow between the left and right hemispheres was thought to be resolved, resulting in spontaneous remission of manic symptoms. Since blood flow and neuronal

firing are linked, this phenomenon was thought to be possible. Abnormal functional connectivities between the orbitofrontal cortex, amygdala, and striatum have been postulated in mania, and in this case, the blood flow imbalance caused by the stroke may have altered these functional connections.[15] A limitation of the present discussion, however, is that no SPECT was performed in this case, and thus, no proof of blood flow imbalance has been provided. Another possibility is that prior infection with COVID-19 affected brain function and induced mania. Moreover, the possibility cannot be ruled out that this patient's stroke was caused by other factors besides COVID-19 infection, such as arteriosclerotic atheroma or hypotension as a systemic symptom of viral infection. However, this hypothesis is rejected by the fact that brain function was normal after the patient fully recovered from COVID-19 infection, and the timing of the mania coincided with the timing of the cerebral infarction detected by MRI. Although mania after stroke is rare, accumulation and analysis of such cases may provide insight into the mechanism of mania.

Conclusion

Elderly people after COVID-19 infection are prone to physical, psychological, and social problems, and physical pathology may be hidden in psychiatric symptoms. The development of strokes should be noted in elderly patients after COVID-19 infection. Multiple right-dominant strokes can cause mania, and the mechanism of poststroke mania needs to be investigated in the future.

Ethical statements

Consent for this report was obtained in accordance with the Declaration of Helsinki and in consideration of patient anonymity. The Ethics Committee of the Sunlight Brain Research Center gave its consent for this report (approval number 23-4).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kurian C, Mayer S, Kaur G, Sahni R, Feldstein E, Samaan M, *et al*. Bihemispheric ischemic strokes in patients with COVID-19. Brain Circ 2022;8:10-6.
2. Huffman JC, Stern TA. Poststroke neuropsychiatric symptoms and pseudoseizures: A discussion. Prim Care Companion J Clin Psychiatry 2003;5:85-8.
3. Shoaib M, Aadil M. Assessment of poststroke mania and diagnosis. Neuropsychiatr Dis Treat 2017;13:557-8.
4. Nagamine T. Omicron variant infections and multiple strokes in older adults. Geriatr Gerontol Int 2023;23:241-2.
5. Nagamine T. Foreign accent syndrome associated with left insula infarction after COVID-19 pneumonia. CJEM 2021;23:858-9.
6. Avila J, Long B, Holladay D, Gottlieb M. Thrombotic complications of COVID-19. Am J Emerg Med 2021;39:213-8.
7. Kihira S, Schefflein J, Mahmoudi K, Rigney B, N Delman B, Mocco J, *et al*. Association of coronavirus disease (COVID-19) with large vessel occlusion strokes: A case-control study. AJR Am J Roentgenol 2021;216:150-6.
8. Divani AA, Andalib S, Di Napoli M, Lattanzi S, Hussain MS, Biller J, *et al*. Coronavirus disease 2019 and stroke: Clinical manifestations and pathophysiological insights. J Stroke Cerebrovasc Dis 2020;29:104941.
9. Sadeghmousavi S, Rezaei N. COVID-19 infection and stroke risk. Rev Neurosci 2021;32:341-9.
10. Santos CO, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: A systematic review. Cerebrovasc Dis 2011;32:11-21.
11. Kang SY, Paik JW, Sohn YH. Restlessness with manic episodes due to right parietal infarction. J Mov Disord 2010;3:22-4.
12. Harmon-Jones E, Abramson LY, Sigelman J, Bohlig A, Hogan ME, Harmon-Jones C. Proneness to hypomania/mania symptoms or depression symptoms and asymmetrical frontal cortical responses to an anger-evoking event. J Pers Soc Psychol 2002;82:610-8.
13. Shi J, Guo H, Liu S, Xue W, Fan F, Fan H, *et al*. Resting-state functional connectivity of neural circuits associated with primary and secondary rewards in patients with bipolar disorder. Soc Cogn Affect Neurosci 2020;15:755-63.
14. Zeng V, Lizano P, Bolo NR, Lutz O, Brady R Jr., Ivleva EI, *et al*. Altered cerebral perfusion in bipolar disorder: A pCASL MRI study. Bipolar Disord 2021;23:130-40.
15. Soto-Vega JG, Valencia JG, Vargas C, López-Jaramillo C. Resting-state functional nuclear magnetic resonance imaging in patients with bipolar disorder: Beyond euthymia. Rev Colomb Psiquiatr (Engl Ed) 2022;51:153-7.