



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com



Case Report

Acute delirium as an initial manifestation of COVID-19 patients with acute ischemic stroke: Report on two cases

Jin-An Huang^{a,b}, Wen-Hsien Chen^{c,d,e}, Nien-Chen Liao^{a,f},
Chieh Liang Wu^f, Yun-Ching Fu^g, Po-Lin Chen^{a,h,*}

^a Division of Neurology, Neurological Institute, Taichung Veterans General Hospital, Taichung, Taiwan

^b Department of Health-Business Administration, Hungkuang University, Taichung, Taiwan

^c Department of Radiology, Taichung Veterans General Hospital, Taichung, Taiwan

^d Department of Industrial Engineering and Enterprise Information, Tunghai University, Taichung, Taiwan

^e Department of Medical Imaging and Radiological Sciences, Central Taiwan University of Science and Technology, Taichung, Taiwan

^f Department of Critical Care Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

^g Deputy Superintendent, Taichung Veterans General Hospital, Taichung, Taiwan

^h Institute of Brain Science, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Received 6 September 2021; received in revised form 12 December 2021; accepted 23 January 2022

KEYWORDS

Acute delirium;
Acute ischemic
stroke;
COVID-19;
Hypercoagulopathy

Psychiatric and neurological complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are common. Psychiatric symptoms are so common that they are easily misinterpreted as an affective disorder induced by SARSCoV-2 infection. However, psychiatric symptoms, such as acute delirium, though rarely seen, can be the initial manifestations of acute ischemic stroke (AIS). These psychiatric symptoms may confuse the diagnosis of acute stroke, which needs correct and timely management. We report two hospitalized cases with SARS-CoV-2 infection and elevated serum D-dimer levels having acute delirium as the initial manifestation of AIS. The diagnostic processes were challenging and time-consuming, so reperfusion therapy could not be given in the therapeutic time window. The diagnoses of AIS were finally made by brain magnetic resonance imaging which showed diffusion restriction at the right middle cerebral artery territory in both cases. Features of psychiatric complications and stroke in coronavirus disease 2019 (COVID-19) patients are reviewed. For the hospitalized COVID-19 patients with elevated levels of serum D-dimer and acute delirium, acute stroke with neuropsychiatric manifestations should be considered. Copyright © 2022, Formosan Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author. Neurological Institute, Taichung Veterans General Hospital, , 1650, Section 4 Taiwan Boulevard, Taichung, 407, Taiwan. Fax: +886 4 23595046.

E-mail address: boringt@gmail.com (P.-L. Chen).

Introduction

Psychiatric manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are common.¹ These complications include depression, anxiety, post-traumatic stress disorder symptoms, and manic-like symptoms, possibly mediated by the significant psychological stress experienced by these patients² and possible effects of SARS-CoV-2 infection on the stress-inflammation cascade.^{1,3} In COVID-19 patients, the prevalence of impaired consciousness is known to be 8–9%,⁴ and agitation or delirium to be 65–69%.⁵ On the other hand, neurological complications of SARS-CoV-2 infection are also common,^{5,6} including ischemic and hemorrhagic stroke, encephalitis, encephalopathy of various causes, seizures, and peripheral inflammatory neuropathy.^{5–7} These neurological complications may manifest with psychiatric symptoms that confuse diagnosis and management.^{4,8} Delayed management of these neurological complications may negatively affect the outcomes. Among these neurological complications of SARS-CoV-2 infection, stroke has much higher mortality than those with other neurological complications.^{7,9} For COVID-19 patients with acute ischemic stroke (AIS), a correct and timely diagnosis of the underlying etiology is essential to start adequate management, including intravenous thrombolysis and endovascular thrombectomy. Here, we presented two hospitalized COVID-19 patients complicated with AIS and their initial presentations with psychiatric manifestations at the isolation ward for SARS-CoV-2 patients.

Cases report

Case 1

An 82 years old male with hypertension, diabetes, hyperlipidemia, and smoking history had a cough for three days. On the fourth day, he had fever and dyspnea. Chest x-ray (CXR) at the emergency department (ED) revealed infiltration over the right lower lung field. The reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) test for SARS-CoV-2 was positive. He was admitted to the intensive care unit (ICU) with tracheal intubation.

Laboratory examinations showed normal prothrombin time (PT), activated partial thromboplastin time (APTT), and serum troponin-T, but an elevated serum level of D-dimer (>35.2 mg/l) and high sensitivity C-reactive protein (hsCRP) of 17.15 mg/dl in serum. He was treated with tocilizumab, dexamethasone, combined with a regimen of antibiotics with ceftriaxone and moxifloxacin, remdesivir, and a prophylactic dosage of low molecular weight heparin (LMWH) with enoxaparin 40 mg daily. On day 6 after symptoms onset, CXR showed partial resolution of pneumonia, and hsCRP decreased to 3.58 mg/dl. But the serum level of D-dimer remained high (23.8 mg/l). On day 7, he was found restless and agitated. He was diagnosed with acute delirium from SARS-CoV-2 infection. Unfortunately, 4 h later, he developed an acute weakness of the left limbs. He was tentatively diagnosed with left lacunar syndrome upon neurological consultation. Soon after, three episodes of focal clonus occurred over the right limbs. He was

urgently transported to the brain computed tomography (CT) suite by the well-equipped medical team via a pre-planned route of green passage. Brain CT angiography (CTA) revealed severe focal stenosis at M1 segment of the right middle cerebral artery (MCA) with post-stenotic dilatation and severe focal stenosis at the P2 segment of the right posterior cerebral artery (PCA) (Fig. 1A). Brain CT nevertheless showed no signs of acute intracranial abnormality, except an old lacunar infarction at the left basal ganglia and bilateral corona radiata, and signs of bone defect at the left parietal skull. We were unsure if the acute left hemiparesis was caused by an acute encephalopathy with seizures. Possibilities of other stroke mimics, like vasculitis, encephalitis, and posterior reversible encephalopathy syndrome (PRES), were not ruled out either. Therefore, we again transported the patient to the magnetic resonance imaging (MRI) suite for brain MRI and MR angiography (MRA). Results of diffusion-weighted imaging (DWI) revealed a diffusion restriction at the right centrum semiovale and frontoparietal cortex compatible with AIS, in addition to severe focal stenosis of the right MCA at the M1 segment and of the right PCA at the P2 segment (Fig. 1B).

His score on the National Institute of Health Stroke Scale (NIHSS) was 5. However, intravenous thrombolysis was not performed because the time from symptom onset to diagnosis exceeded the therapeutic time window. A 12-lead electrocardiogram showed sinus tachycardia with nonspecific T wave abnormalities. The transthoracic echocardiogram (TTE) showed mild mitral and aortic regurgitation with normal wall motion of the left ventricle. The plasma low-density lipoprotein (LDL) was 102 mg/dl. Immunological studies were normal, including antinuclear antibodies, anti- β 2-glycoprotein I antibodies, and anticardiolipin antibodies. Dual antithrombotics, including aspirin and enoxaparin, atorvastatin, and levetiracetam, were applied. His neurological status remained stable during the following week. He was finally transferred to the isolation ward for further care.

Case 2

An 84 years old male with hypertension, diabetes, and smoking history had fever, cough, and dyspnea for two days. CXR revealed infiltration over lower lung fields on both sides. His RT-qPCR test for SARS-CoV-2 was positive. Laboratory examinations showed normal PT, APTT, and serum troponin-T, but a mildly elevated serum level of D-dimer (0.63 mg/l; normal range < 0.55 mg/l) and hsCRP of 6.70 mg/dl in serum. He was treated with tocilizumab, dexamethasone, combined regimens of antibiotics with ceftriaxone and levofloxacin, and remdesivir. We also prescribed a prophylactic dosage of LMWH with enoxaparin 40 mg daily.

He remained stable till day 13 after symptoms onset, when he suddenly turned irritable and agitated first, then became depressed and was crying. CXR showed complete resolution of pneumonia, and serum hsCRP was normal (0.19 mg/dl). He was tentatively diagnosed with ICU-like psychosis upon psychiatric consultation. Anxiolytics and antidepressants were prescribed. Four days later, his D-dimer level increased further to 14.15 mg/l. On day 19 after

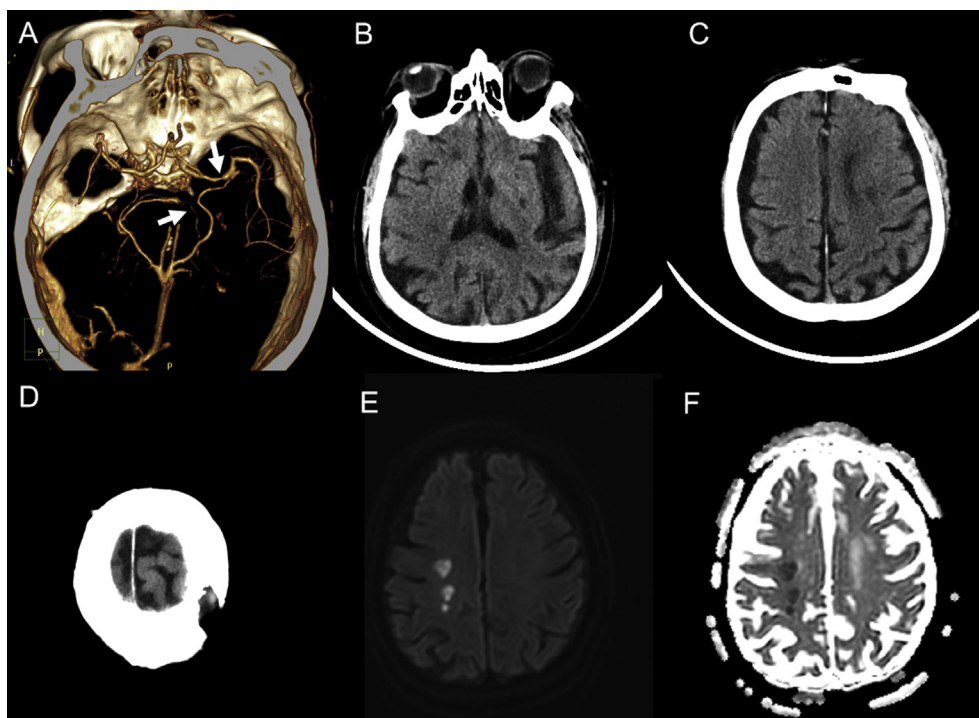


Figure 1 (A) Brain computed tomography (CT) angiography showed severe focal stenosis at M1 segment of the right middle cerebral artery with post stenotic dilatation and severe focal stenosis at the P2 segment of the right posterior cerebral artery. (B) and (C) Brain CT showed old lacunar infarction at left basal ganglia and bilateral corona radiata. (D) A bone defect at the left parietal skull was noted. (E) and (F) Brain magnetic resonance imaging showed a diffusion restriction on diffusion-weighted imaging at the right centrum semiovale.

COVID-19 symptoms onset, he developed left side hemiparesis. Because of the concern on the sensitivity of brain CT for early ischemic lesions, we immediately transported the patient to the MRI suite for brain MRI and MRA to make the diagnosis correctly and timely. Brain MRI/MRA revealed, on DWI, diffusion restrictions at the right corona radiata, external capsule, right posterior temporal lobe, and right temporal uncus. Findings were compatible with a recent infarction over the right MCA territory (Fig. 2). In addition, severe stenosis was observed over the right distal MCA, right distal PCA, and left distal PCA. His plasma LDL was 85 mg/dl. A 12-lead electrocardiogram showed normal sinus rhythm. TTE showed left atrial enlargement with a diameter of 5.2 cm, mild mitral and aortic regurgitation, mild hypertrophy, and normal wall motion of the left ventricle. Immunological studies were normal, including antinuclear antibodies, anti- β 2-glycoprotein I antibodies, and anti-cardiolipin antibodies. Enoxaparin was then replaced with edoxaban 30 mg daily. Left hemiparesis gradually improved, and he was discharged with a good functional recovery.

Discussion

We reported two hospitalized cases of SARS-CoV-2 infection having acute delirium as the initial manifestation of AIS. In both cases, acute delirium preceded limb weakness. The diagnostic processes were challenging and time-consuming, so reperfusion therapy could not be given in the therapeutic time window.

Neuropsychiatric symptoms, such as delirium, delusion, or mania, appear in about 3% of stroke patients.¹⁰ The prevalence of acute delirium after acute stroke varies according to different regions and assessment tools used.^{11–13} Fourteen to thirty percent of patients with an acute stroke developed acute delirium. Because cognitive abnormalities are so common,^{4,5} they are easily misinterpreted as depression or considered as an affective disorder.⁸ Risk factors of acute delirium after acute stroke include higher NIHSS scores, previous stroke, leukoencephalopathy, concurrent infection, stroke subtype of large artery atherosclerosis, and a cortical infarct or aphasia.^{11,12} AIS occurs in approximately 1–3% of COVID-19 patients.⁶ About 40–60% of COVID-19 patients complicated with ischemic stroke have large vessel occlusion.^{14,15} In our report, both patients had an AIS subtype of large artery atherosclerosis involving cortices which are at risk for acute delirium in COVID-19 patients with AIS.

In the SVIN COVID-19 multinational registry,¹⁶ the most frequently reported etiology of AIS is cryptogenic (42.6%), associated with significantly higher white blood cell count, elevated levels of c-reactive protein, and D-dimer compared with non-cryptogenic AIS patients. In our report, both COVID-19 patients with acute delirium had elevated serum D-dimer. In addition to hypercoagulopathy,⁹ brain MRI in SARS-CoV-2 infection may demonstrate evidence of cerebral endotheliitis,¹⁷ including enhanced cerebral arteries, extensive cerebral vasculitic lesions in a combined pattern of ischemia, hemorrhage, white matter-enhancing lesions, or punctuate postcontrast enhancement.¹⁷

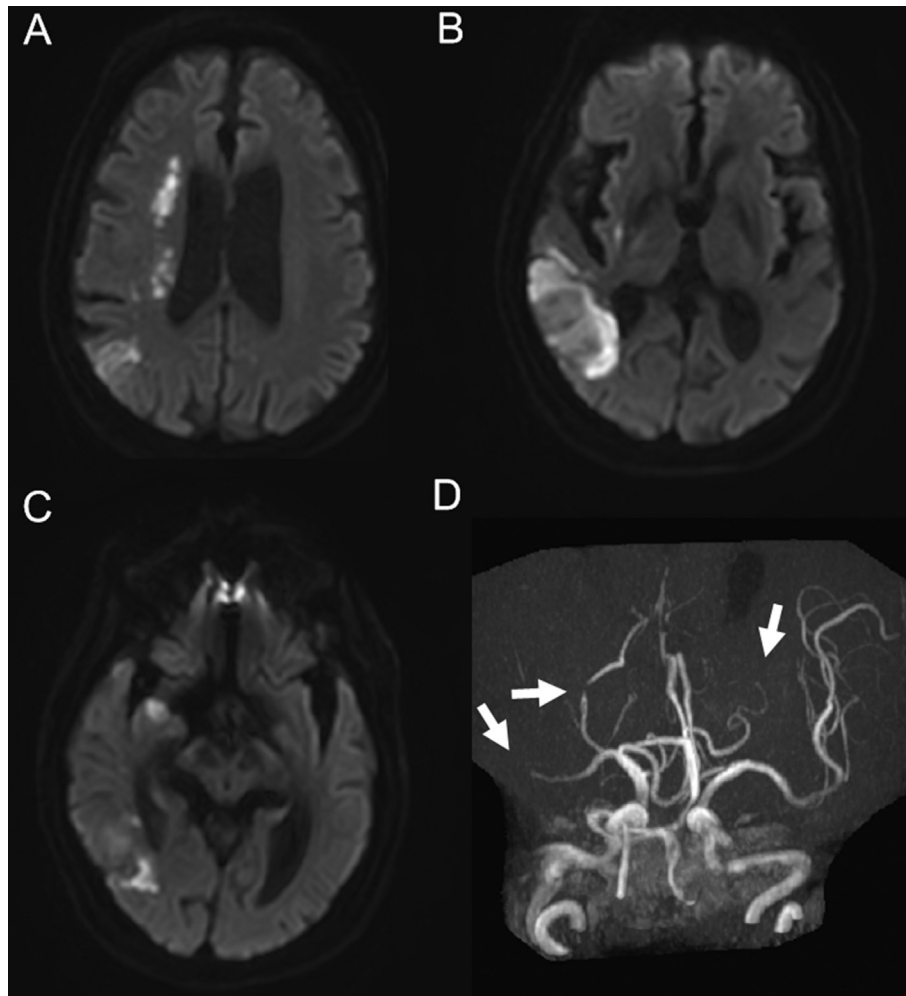


Figure 2 (A)–(C) Brain magnetic resonance imaging of Case 2 showed diffusion restrictions on diffusion-weighted imaging at right corona radiata, external capsule, right posterior temporal lobe, and right temporal uncus. (D) Brain magnetic resonance angiography showed severe stenosis over the right distal middle cerebral artery, right distal posterior cerebral artery (PCA), and left distal PCA.

About 1/3 of COVID-19 patients with neurological manifestations who were referred for neuroimaging showed brain abnormalities.¹⁸ Brain CT is typically the preferred initial imaging modality for acute stroke during the COVID-19 pandemic. However, brain CT is not sensitive to early ischemic lesions. Because acute delirium is independently associated with poor outcome and mortality in acute stroke,¹³ early and timely management in such patients is crucial. Patients with stroke may present with various atypical or non-localizing symptoms which are clinically hard to differentiate from stroke mimics.¹⁹ Differentiation is challenging when acute encephalopathy or neuropsychiatric symptoms are present. Although MRI is often used to confirm a diagnosis of AIS, it is more complex and time-consuming than CT. The American College of Radiology recommends minimizing the use of MRI in the COVID-19 pandemic except when absolutely necessary.²⁰ In the COVID-19 pandemic, CT became predominant as an emergency brain imaging tool before reperfusion therapy due to the limitation of using MRI for patients with negative SARS-CoV-2 PCR.²¹ However, brain

MRI has a distinct advantage in identifying stroke mimics and narrows the differential diagnoses than the CT-based workup.²² A case report of COVID-19 described a patient with acute encephalopathy with loss of consciousness.²³ The non-contrast brain CT failed to show any acute intracranial abnormalities. However, brain MRI revealed multiple sites of restricted diffusion on DWI across multiple lobes. Such findings are consistent with AIS. Brain MRI is also valuable for detecting other abnormalities in COVID-19 encephalopathies, such as acute tumefactive demyelination and PRES,²⁴ which might show unremarkable findings on the brain CT. For Case 1, we adopted brain CT to reduce the risk of accidental dissemination of SARS-CoV-2 based on familiarity and the efficient imaging process. However, the unremarkable brain CT demanded a second brain MRI to confirm the diagnosis, which significantly prolonged the diagnostic process, making the reperfusion therapy unqualified. For Case 2, instead of brain CT, we performed brain MRI which revealed a recent infarct over the right MCA territory, compatible with the onset time of neuropsychiatric manifestations.

The mechanisms of AIS in COVID-19 patients are multifactorial,²⁵ including prothrombotic effects from conventional vascular risk factors, infection-induced systemic inflammatory response, endotheliitis, dysregulation of the axis of angiotensin II and angiotensin 1-7, and excessive cytokine release. In addition, SARS-CoV-2 infection may result in decreased intake, dehydration, poor medication adherence, and subsequent thrombosis in high-risk patients. Both patients of our report, having traditional vascular risk factors and significant stenosis of intracranial cerebral arteries, are possibly vulnerable to the above mechanisms which cause subsequent superimposed thrombosis. At the onset of AIS, the serum levels of D-dimer remained elevated, although pneumonia resolved with decreased or normalized serum levels of hsCRP. Thus, we presumed that hypercoagulopathy from SARS-CoV-2 infection is the cause of AIS in our patients.

In conclusion, isolated COVID-19 patients are at high risk of developing stroke. For COVID-19 patients with elevated serum levels of D-dimer and acute delirium, unexplained neurological findings, or ambiguously non-localizing signs, acute stroke should be considered. A preplanned route of green passage for transportation of the patients to the brain MRI suite may reduce the risk of accidental dissemination of SARS-CoV-2 and ensure correct and timely diagnosis of acute stroke.

Funding information

The authors have no funding to declare relevant to this article.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

We thank everyone at TCVGH who made great efforts in COVID-19 prevention and treatment during the pandemic, especially to all who worked in the isolation wards and infection control staff.

References

- Jansen van VE, Steyn SF, Brink CB, Moller M, Viljoen FP, Harvey BH. The neuropsychiatric manifestations of COVID-19: interactions with psychiatric illness and pharmacological treatment. *Biomed Pharmacother* 2021;135:111200.
- Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. *Brain Behav Immun* 2020;88:17–27.
- Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci* 2012;1261:55–63.
- Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. *J Neurol Sci* 2020;413:116832.
- Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020;382:2268–70.
- Sharifian-Dorche M, Huot P, Oshero M, Wen D, Saveriano A, Giacomini PS, et al. Neurological complications of coronavirus infection: a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci* 2020;417:117085.
- Chowdhary A, Subedi R, Tandon M, Wen S, Patel J, Kataria S, et al. Relevance and clinical significance of magnetic resonance imaging of neurological manifestations in COVID-19: a systematic review of case reports and case series. *Brain Sci* 2020;10.
- Huffman J, Stern TA. Acute psychiatric manifestations of stroke: a clinical case conference. *Psychosomatics* 2003;44:65–75.
- Tan YK, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis* 2020;50:587–95.
- Dunne JW, Leedman PJ, Edis RH. Inobvious stroke: a cause of delirium and dementia. *Aust N Z J Med* 1986;16:771–8.
- Qu J, Chen Y, Luo G, Zhong H, Xiao W, Yin H. Delirium in the acute phase of ischemic stroke: incidence, risk factors, and effects on functional outcome. *J Stroke Cerebrovasc Dis* 2018;27:2641–7.
- Rollo E, Callea A, Brunetti V, Vollono C, Marotta J, Imperatori C, et al. Delirium in acute stroke: a prospective, cross-sectional, cohort study. *Eur J Neurol* 2021;28:1590–600.
- Pasinska P, Wilk A, Kowalska K, Szyper-Maciejowska A, Klimkiewicz-Mrowiec A. The long-term prognosis of patients with delirium in the acute phase of stroke: PROspective Observational POLish Study (PROPOLIS). *J Neurol* 2019;266:2710–7.
- Ladopoulos T, Zand R, Shahjouei S, Chang JJ, Motte J, Charles JJ, et al. COVID-19: neuroimaging features of a pandemic. *J Neuroimaging* 2021;31:228–43.
- Khedr EM, Soliman RK, Abo-Elfetof N, Amin M, Mansour OY, Aly A, et al. Clinical and radiological characteristics of acute cerebrovascular diseases among Egyptian patients with COVID-19 in upper Egypt. *Front Neurol* 2021;12:635856.
- Ramos-Araque ME, Siegler JE, Ribo M, Requena M, Lopez C, de Lera M, et al. Stroke etiologies in patients with COVID-19: the SVIN COVID-19 multinational registry. *BMC Neurol* 2021;21:43.
- Hanafi R, Roger PA, Perin B, Kuchcinski G, Deleval N, Dallery F, et al. COVID-19 neurologic complication with CNS vasculitis-like pattern. *Am J Neuroradiol* 2020;41:1384–7.
- Egbert AR, Cankurtaran S, Karpiak S. Brain abnormalities in COVID-19 acute/subacute phase: a rapid systematic review. *Brain Behav Immun* 2020;89:543–54.
- Edlow JA, Selim MH. Atypical presentations of acute cerebrovascular syndromes. *Lancet Neurol* 2011;10:550–60.
- ACR guidance on COVID-19 and MR use. 2021. <https://www.acr.org/Clinical-Resources/Radiology-Safety/MR-Safety/COVID-19-and-MR-Use>.
- Koge J, Shiozawa M, Toyoda K. Acute stroke care in the with-COVID-19 era: experience at a comprehensive stroke center in Japan. *Front Neurol* 2020;11:611504.
- Rowley H, Vagal A. Stroke and stroke mimics: diagnosis and treatment. In: Hodler J, Kubik-Huch RA, von Schulthess GK, editors. *Diseases of the brain, head and neck, spine 2020-2023: diagnostic imaging cham*. CH; 2020. p. 25–36.
- Prasad A, Kataria S, Srivastava S, Lakhani DA, Sriwastava S. Multiple embolic stroke on magnetic resonance imaging of the brain in a COVID-19 case with persistent encephalopathy. *Clin Imag* 2021;69:285–8.
- Agarwal A, Pinho M, Raj K, Yu FF, Bathla G, Achilleos M, et al. Neurological emergencies associated with COVID-19: stroke and beyond. *Emerg Radiol* 2020;27:747–54.
- Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: a systematic review and meta-analysis. *Int J Stroke* 2021;16(2):137–49.