COVID-19 Infection and Recurrent Stroke in Young Patients With Protein S Deficiency

A Case Report

Leila Ali, MD,*†‡ Hela Jamoussi, MD,*†‡ Nessrine Kouki, MD,* Saloua Fray, MD,*†‡ Slim Echebbi, MD,*†‡ Nadia Ben Ali, PhD,*†‡ and Mohamed Fredj, PhD*†‡

Introduction: Protein S deficiency and coronavirus disease 2019 (COVID-19) are rare etiologies of ischemic stroke. We describe a case of an ischemic stroke revealing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in a patient with a history of protein S deficiency and cerebral imaging suggestive of vasculitis.

Case Report: A 52-year-old woman, with history of protein S deficiency, was admitted for right hemiparesis and aphasia that happened 6 hours before her consultation. Her National Institutes of Health Stroke Scale (NIHSS) was 11. She had hypoxia (SpO2 93%). COVID-19 polymerase chain reaction was positive. Cerebral computed tomography scan showed an ischemic stroke in the territory of the superficial left middle cerebral artery. The recommended time period for thrombolysis was exceeded and an ischemic stroke in the territory of the superficial left middle cerebral artery was confirmed. The patient was treated with aspirin, statins, antibiotic therapy, and oxygen. Considering the high risk of thromboembolic complications and the history of protein S deficiency, anticoagulation treatment with heparin followed by acenocoumarol was started. Evolution was marked by the appearance of 24 hours regressive, acute symptoms of confusion. Brain magnetic resonance imaging showed new ischemic strokes in both anterior cerebral arteries and on magnetic resonance angiography narrowing of the left internal carotid artery and both anterior cerebral arteries suggestive of vasculitis were seen. We maintained anticoagulation and prescribed methylprednisolone 500 mg daily for 3 days. Evolution was marked by improvement of clinical deficit and respiratory status.

Conclusions: SARS-CoV-2 infection potentiates the prothrombotic effect and vascular inflammation by accentuating protein S deficit. The place of steroids seems justifiable in the presence of symptoms of vasculitis in brain imaging.

Key Words: case report, stroke, COVID-19, protein S, vasculitis, corticosteroids

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The prevalence of protein S deficiency as an etiology of ischemic stroke is low: 5% to 11%, and is one of ischemic stroke due to coronavirus disease 2019 (COVID-19). The morbidity and mortality of COVID-19 are often associated with cardiovascular risk factors. Recent studies have shown that systemic thromboembolism is the principal mechanism of the disease. In this case, we describe an ischemic stroke revealing COVID-19 infection, in a patient with a history of protein S deficiency and we discuss a possible association with vasculitis.

CASE REPORT

A 52-year-old woman, with history of hypothyroidism and 2 episodes of superficial vein thrombosis in relation with hereditary protein S deficiency, was admitted to our department for abrupt weakness of her right side with aphasia happened 6 hours before her consultation. Neurological examination found right hemiparesis and aphasia. An initial National Institutes of Health Stroke Scale (NIHSS) was 11 (language: 3, right arm: 4, right leg: 2, facial palsy: 2; it was difficult to assess sensory loss and visual disturbance considering aphasia). Physical examination showed moderate hypoxia (SpO2 93%). Otherwise, she had no symptoms of fever, or any other signs of COVID-19 including anosmia, aguesia, cough, bowel disturbance, fatigue, or muscle and joint pain. There were also no signs of other vascular peripheral occlusion. Biological examination showed a persistent increase in C reactive protein (CRP) of 65 mg/L, elevated D-dimers of 7.47 µg/mL controlled 24 hours later at 25 µg/mL, and elevated fibrinogen of 7 g. The first cerebral computerized tomography (CT) showed normal. Polymerase chain reaction nasopharyngeal swab of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was positive. Thoracic CT scan showed ground glass opacities and concluded to be moderate SARS-CoV-2 parenchymal lesions and excluded pulmonary embolism (Fig. 1). A second cerebral CT scan (H24) showed a hypodensity at the superficial left middle cerebral artery territory (Fig. 2). Electrocardiogram and cardiac echography were normal. Screening for autoimmune diseases and antiphospholipid syndrome was negative. Our patient consulted after the recommended timeline for thrombolysis and we did not dispose of sufficient resources to deliver thrombectomy. So, she was treated initially with aspirin, statins, famotidine, azithromycin, cefpodoxime, vitamin D, vitamin C, zinc, and oxygen therapy. Considering the high risk of thromboembolic complications in our patient and the history of protein S deficiency, we decided to start therapeutic anticoagulation with heparin low molecular weight and then with acenocoumarol 3 mg daily at day 6 after a control cerebral CT scan showed the same aspect of a minor stroke and excluded hemorrhagic complication. Evolution was marked by improvement of respiratory symptoms with SpO2 98% at ambient air. Six days after initiation of anticoagulation, the patient developed 24 hours regressive, acute symptoms of confusion, agitation and aggressivity. Biological examination showed a persistent inflammation with a CRP of 100 mg/L, prothrombin time at 16%, and the international normalized ratio level was 3.93. We performed brain magnetic resonance imaging that excluded bleeding, but showed new ischemic strokes in both anterior cerebral arteries. Cerebral angiography showed narrowing of the left internal carotid artery, and both anterior cerebral arteries with no visible intraluminal thrombosis suggestive of vasculitis. Evolution was marked by a major improvement in clinical deficit and decrease in NIHSS score to 2 (language: 2, right arm: 2, right

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leg: 1, facial palsy: 2). Control biology showed an increase in lymphocyte count to 1200, decrease of inflammation to CRP 37 mg/L, fibrinogen count to 4 g/L, and prothrombin time 24% international normalized ratio 2.48. The patient was discharged with prescription of acenocoumarol 2 mg daily, statins and motor and language rehabilitation. One month later, NIHSS of our patient was 3 (language: 1, right arm: 1, right leg: 0, facial palsy: 1).

DISCUSSION
SARS-CoV-2 infection is described to be responsible for central and peripheral nerve damage. The main symptoms described to be associated with COVID-19 are headache, ischemic and hemorrhagic acute cerebrovascular diseases, olfactory and taste disorders, acute symptomatic seizure, Guillain-Barré syndrome, meningitis, encephalitis, and acute hemorrhagic necrotizing encephalopathy. Prevalence of acute ischemic stroke associated with COVID-19 infection is 1%. COVID-19-associated stroke has some specificities: in most reported cases stroke occurred with a median of 10 days from COVID-19 onset but in some cases, stroke was the first manifestation. Patient with COVID-19 seemed to be particularly prone to large vessel occlusion and multiterritory involvement like in our patient. In our case, it was recurrent stroke despite therapeutic anticoagulation. One similar case was reported by Beyrouti et al.

The possible mechanisms that evoked central nervous system damage due to COVID-19 are the following.

- Cytokine storm: an immune reaction secondary to elevated levels of cytokines and chemokines mainly interleukin (IL)-6, IL-1 beta, interferon gamma, tumor necrosis factor, resulting in systemic inflammation and multiorgan damage.

An elevated level of von Willebrand factor was found in patients with SARS-CoV-2 and this factor is associated with endothelial damage.

- Cell invasion that is maintained by the transmembrane spike (S) glycoprotein, which has 2 active subunits S1 and S2. S1 binds to the angiotensin-converting enzyme 2 (ACE2) host cell receptor and S2 fuses the cellular and viral membranes. ACE2 is expressed in the neurons, glial cells of the brain stem, and in the cardiovascular system. This viral attachment to ACE2 receptors in endothelial cells causes a thrombotic state by widespread endotheliitis, coagulopathy, and by large vessel occlusion.

- Dysfunction of the blood-brain barrier: due to the activation of infected astrocytes and microglia in the cerebrum, and due to the dysfunction of the microvasculature through endotheliitis.

- Cerebral hypoperfusion: a postinfectious COVID-19 complication which was reported in some cases of the literature. It is consistent with orthostatic hypoperfusion syndrome (chronic fatigue, orthostatic dizziness, and brain fog). This syndrome is associated with reduced orthostatic cerebral blood flow and
signs of cerebral hypoperfusion without orthostatic hypotension or orthostatic tachycardia. The mechanism suggested for this syndrome is a possible failure of cerebral autoregulation due to abnormal cerebral arteriolar vasoconstriction and immune-mediated arteriolar dysfunction.12

Correlating these data with the case of our patient, we suppose that the main mechanisms that could lead to recurrent strokes may be due to cytokine storm, dysfunction of the blood-brain barrier leading to endotheliitis and to a thrombotic state.

Thromboembolic events due to COVID-19 have been described in one-third of seriously ill patients. Some studies demonstrated occurrence of protein S deficiency after SARS-CoV-2 infection.13 This association can be explained by 2 possible mechanisms: The disseminated intravascular clotting which could be responsible for secondary decrease of protein S level among many other coagulation factors and the structural similarities between spike protein and protein S. In fact, after SARS-CoV-2 infection, antibody seroconversion occurs during the second week resulting in the synthesis of antiprotein spike antibodies, which can lead to secondary protein S deficiency.13

Another recent hypothesis have stipulated the possible role of protein S as an activating ligand for the TAM family of receptor tyrosine kinases (RTKs)—TYRO3, AXL, and MER (also known as MERTK) in association with GAS6. This was required to maintain vascular integrity by strengthening of tight junctions.15 Some cases of West Nile virus infection, induced endothelial cells to express protein S-activated MER. Protein S and GAS6 fixation on the extracellular domain of MER on immune cells (macrophages and dendritic cells) decreases the production of cytokines and chemokines which will prevent autoimmune response.15 Protein S deficiency induces low signaling of TAM receptors and as a result chronic immune activation with a possible development of autoimmune diseases such as systemic lupus erythematosus.15 Similarly and due to the intricate connection between SARS-CoV-2 and protein S, we suppose the presence of a similar mechanism in inducing vasculitis.

In our case, the multifocal narrowing found on cerebral angiography was suggestive of vasculitis or of reversible cerebral vasoconstriction syndrome (RCVS). But considering clinical and imaging data we concluded it to be central nervous system vasculitis. In fact, our patient did not have thunderclap headache like typically described in RCVS.15 Infarcts in RCVS are often bilateral and symmetrical, located in arterial watershed regions of the cerebral hemispheres, whereas in our patient, infarcts were located in the territory of the anterior cerebral arteries. In addition, the narrowing found was not followed by abnormal dilated segments like typically found in RCVS.15 We did not perform lumbar puncture because the patient was under anticoagulation. The improvement after treatment with corticosteroids was also suggestive of this diagnosis.

In a neuropathologic study of brain autopsy of SARS-CoV-2-infected patients published in *Neuropathology and Applied Neurobiology*, the authors reported the presence of intracerebral endotheliitis in 2 patients among 6. They also found higher ACE2, the SARS-CoV-2 receptor, expression in the brain vasculature of patients with endotheliitis than in COVID-19 patients without endotheliitis or than in control patients.16 Another histologic study of different organs in a series of patients with COVID-19 published in *The Lancet* found evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation.11 The observed endotheliitis could be an autoimmunity, late-onset phenomenon or a direct effect of endothelial infection.16 In fact, the authors showed the presence of viral elements within the endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death.11 The vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis. Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium toward more vasoconstriction with subsequent organ ischemia, inflammation with associated tissue edema, and a procoagulant state.11 These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with the presence of viral bodies) and of the host inflammatory response. This hypothesis provides a rationale for therapies to stabilize the endothelium while tackling viral replication, particularly with anti-inflammatory anticytokine drugs, ACE inhibitors, and statins.11

As seen in our patient, we suppose that COVID-19 can be responsible for endothelial inflammation on its own. The presence of protein S deficiency facilitates the process even more. We conclude that SARS-CoV-2 infection along with protein S deficiency can be responsible for major thromboembolic events through coagulopathy and chronic immune activation. This might explain the recurrence of strokes in our patient even though she was under efficient anticoagulation.

Treatment of SARS-CoV-2 infection is still empirical, mainly based on assays of treatments that might have competitive structural aspects to the virus entry, or suppressive roles of the virus pathogenicity such as coagulopathy, inflammation,
| References       | Age (y)/Sex | Medical History                                           | Time of Stroke From COVID Onset | Brain Imaging                                                                 | Stroke Implicated Mechanism | Biology                          | Treatment                                      | Outcome                                                                 |
|------------------|-------------|----------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------------|-------------------------------|-----------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------|
| Dixon et al<sup>19</sup> | 64/male     | Type 2 diabetes/hypertension, hypercholesterolemia        | Day 5                         | MRI: multiple subacute infarcts in the right middle cerebral artery (MCA) and both posterior cerebral artery (PCA) territories | Vasculitis                    | D-dimer (µg/L, 0-550), 20,000 | Mechanical ventilation, antithrombotic therapy: prophylactic       | Improvement no new infarcts, reduction in cerebral swelling and persistent abnormal vessel wall enhancement |
|                  |             |                                                         |                               | Angiography: occlusion of the right PCA and left PCA                         |                               | CRP: elevated 196 mg/L          | Corticosteroids: 1 g/d for 5 d then oral prednisolone (60 mg daily) |                                                                 |
|                  |             |                                                         |                               | Postcontrast volume: T1-space MRI sequence revealed long segment, abnormal concentric, vessel wall enhancement of both MCAs, anterior cerebral arteries, vertebral arteries and the basilar artery |                               | Screening for autoimmune diseases and antiphospholipid syndrome: negative | Other: aspirin, levetiracetam was given for seizure management. Acyclovir and ceftriaxone, IL-1 receptor antagonist anakinra was given at a dose of 200 mg 2 times a day, IL-6 antagonist tocilizumab 8 mg/kg intravenous |                                                                 |
| Vaschetto et al<sup>20</sup> | 64/male     | Nothing to report                                         | Day 7                         | CT scan: some cortical-subcortical blood-related hyperdensities in the bilateral frontoparietal and right occipital lobes | Vasculitis, embolic            | D-dimer (µg/L, 0-550); not specified | Mechanical ventilation, antithrombotic therapy: prophylactic        | Significant reduction of the pons ischemia                          |
|                  |             |                                                         |                               | MRL: some signal restriction of the cortex in a parietal and parieto-occipital region and at the pons level suggesting both signs of cortical inflammation and ischemia in the subacute phase |                               | CRP: 4.85 mg/dL                 | Immunoglobulins: 30 g/d for 5 d |                                                                 |
|                  |             |                                                         |                               | MRI: multiple subacute infarcts in the right middle cerebral artery (MCA) and both posterior cerebral artery (PCA) territories |                               | Screening for autoimmune diseases and antiphospholipid syndrome: C3 reduced to 10 mg/dL and C4 to 4 ng/dL and elevated serum beta-2 microglobulin 3080 ng/mL | Corticosteroids: 1 g/d for 5 d |                                                                 |

COVID-19 indicates coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; IL, interleukin; MRI, magnetic resonance imaging.
and cytokine storm. Anticoagulation is the principal treatment of protein S deficiency in case of major ischemic vascular events,\(^\text{17}\) and is proposed as a beneficial treatment for COVID-19 stroke patients.\(^\text{18}\) The association of both affections in one patient justifies even more this therapeutic approach. We even suggest a therapeutic preventive anticoagulation for patients with protein S deficiency during the COVID-19 pandemic to prevent the occurrence of major ischemic events.

The role of steroids seems justifiable in the presence of symptoms of vasculitis in brain imaging. Dixon and colleagues tried a case similar to our patient. Methylprednisolone at a dose of 1 g/d followed by oral prednisolone 60 mg/d and IL-1 receptor antagonist anakinra at a dose of 200 mg twice daily were tried with a stabilization of symptoms and reduction of cerebral swelling.\(^\text{19}\) Vaschetto et al\(^\text{20}\) tried with a similar case, intravenous immunoglobulins at 30 g/d for 5 days and thereafter methylprednisolone 1 g/d for 5 days resulting in an unchanged neurological examination, and in contrast a significant reduction of ischemia in control brain imaging. Cases of stroke due to vasculitis associated with COVID-19 and treated with corticosteroids are reported in Table 1.

Two studies performed in Italy and the United States found that the outcome of COVID-19-related stroke cases was significantly worse than that of non-COVID stroke cases. Predictors of poor outcome were: thrombocytopenia, lymphocytopenia, and elevated levels of D-dimer and lactate dehydrogenase, in addition to those found in non-COVID stroke cases, such as older age, higher NIHSS at admission, baseline glucose, and creatinine levels.\(^\text{7}\)

### CONCLUSIONS

It seems that stroke in the context of COVID-19 infection may have distinct pathogenic mechanisms. SARS-CoV-2 infection potentializes the prothrombotic effect and vascular inflammation by accentuating protein S deficit. This is mainly due to the structural similarities between protein S and spike protein at the surface of the virus. Some management issues specific to this population must be considered. Anticoagulation treatment is justified in this case, and we suggest during this pandemic a preventive anticoagulation even in the absence of history of major vascular ischemic events. The role of steroids seems justifiable in the presence of symptoms of vasculitis in brain imaging.

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