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Acute worsening of CADASIL in a patient with COVID-19 infection: illustrative case

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BACKGROUND Reports of cerebrovascular ischemia and stroke occurring as predominant neurological sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which causes coronavirus disease 2019 (COVID-19), are increasingly evident within the literature. While various pathophysiological mechanisms have been postulated, including hypercoagulability, endothelial invasion, and systemic inflammation, discrete mechanisms for viral neurotropism remain unclear and controversial.

OBSERVATIONS The authors present a unique case study of a 64-year-old male with acute COVID-19 infection and acute worsening of previously stable cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a rare heritable arteriopathy due to mutation in the *Notch3* gene, which is critical for vascular development and tone. Delayed cranial neuropathies, brainstem fluid-attenuated inversion recovery signal, and enhancement of olfactory and vagus nerves on magnetic resonance neurography in this patient further support viral neurotropism via cranial nerves in addition to cerebral vasculature.

LESSONS To the authors' knowledge, this is the first case in the literature that not only demonstrates the consequences of COVID-19 infection in a patient with altered cerebrovascular autoregulation such as CADASIL but also highlights the tropism of SARS-CoV-2 for (1) cranial nerves as a mode of entry to the central nervous system and (2) vessels as a cause of cerebrovascular ischemia.

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KEYWORDS COVID-19; SARS-CoV-2; CADASIL; stroke; coronavirus; vagus nerve

Our understanding of central nervous system involvement in the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still evolving.[1] Stroke has increasingly been reported as a predominant neurological feature of the disease, yet rates of both ischemic and hemorrhagic infarction remain rare overall.[2] While the clinical and economic burdens of stroke from any cause are well established, the precise pathogenesis in SARS-CoV-2–infected patients remains vastly unclear, thereby rendering predictions of vulnerable populations insufficient.[1]

Multiple theories regarding the pathophysiology of ischemic stroke secondary to SARS-CoV-2 infection have been postulated in the literature, including systemic inflammation, promotion of hypercoagulability, and direct endothelial viral invasion.[3–5] Postmortem histopathologic examination of microvascular injury initially identified as punctate hyperintensities on magnetic resonance imaging (MRI) revealed perivascular-activated microglia, macrophages, hypertrophic astrocytes, T-cell infiltration, microhemorrhages, and fibrinogen leakage without thromboembolic occlusion in one such study.[3] While

ABBREVIATIONS ACE2 = angiotensin-converting enzyme 2; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CN = cranial nerve; COVID-19 = coronavirus disease 2019; FLAIR = fluid-attenuated inversion recovery; MR = magnetic resonance; MRI = magnetic resonance imaging; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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some authors propose secondary inflammation, subsequent studies instead demonstrate direct infection of endothelial cells as a key contributory mechanism.[5] As such, common risk factors that predispose patients to increased inflammatory states or endothelial dysfunction, such as diabetes mellitus, hypertension, or congestive heart failure, are heavily monitored for development of multiorgan dysfunction including neurological injury.[6]

Given the heterogeneity of clinical presentation in COVID-19 infection, determining the pathogenesis of cerebral ischemia by SARS-CoV-2 is vital to effectively predict risk factors, manage clinical course, optimize long-term neurological outcomes, and determine worthwhile strategies for both prevention and intervention. A paucity of data ultimately exists for patients with noninflammatory vasculopathies and other heritable cerebrovascular conditions regarding COVID-19 infection, pathophysiology, and outcomes. However, these cases ultimately offer unique insights into the viral mechanism of ischemic stroke. Herein, we report a case of cerebral autosomal dominant arteriopathy with subcortical infarcts and

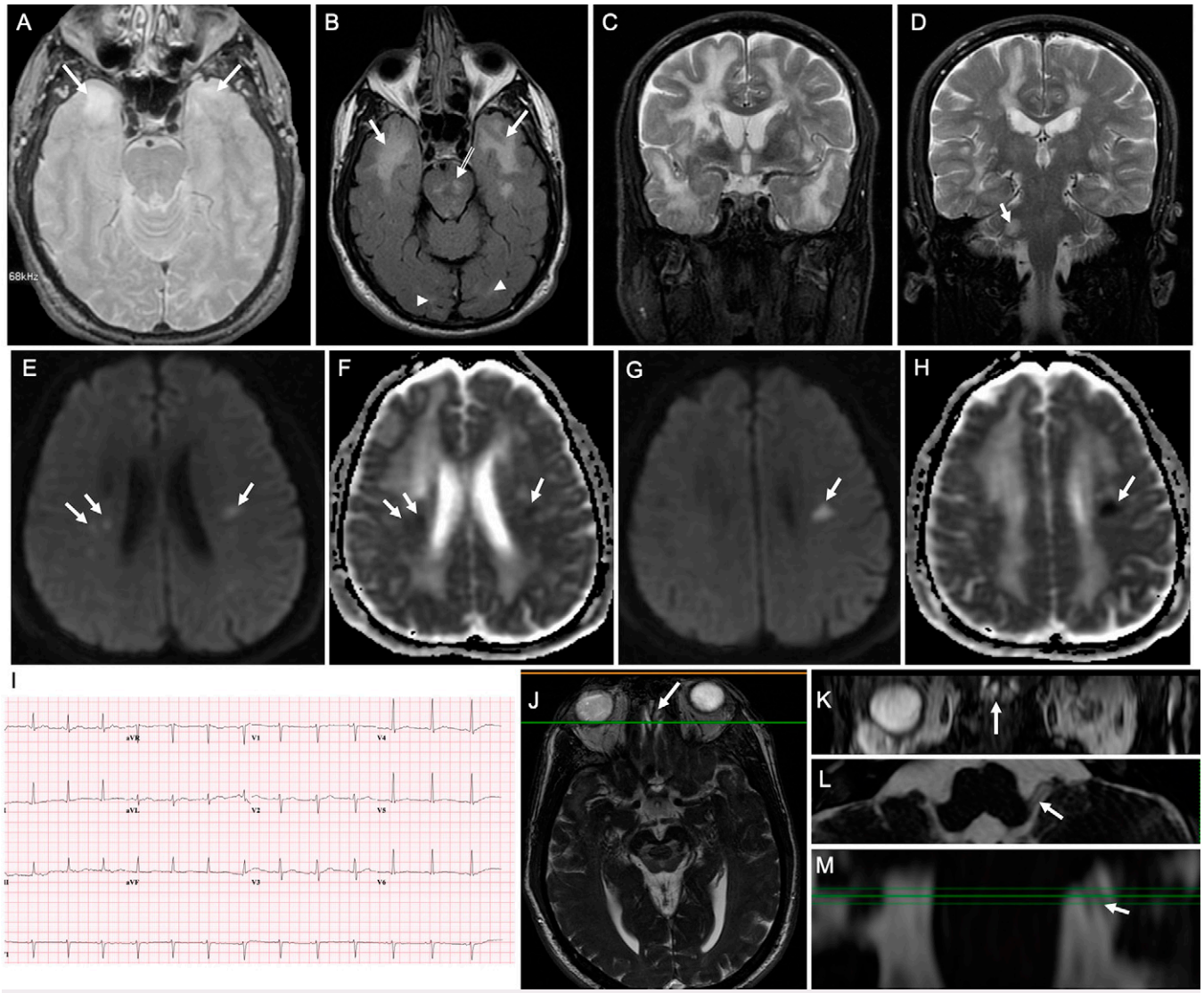

FIG. 1. Imaging and electrocardiographic evaluations. **A:** Baseline T2-weighted axial MRI of the brain from 20 years prior to presentation shows T2 signal hyperintensity (*arrows*) in the anterior temporal lobes. **B:** Axial T2-weighted FLAIR MRI of the brain taken on the day of hospital presentation shows increased T2 signal hyperintensity throughout the anterior temporal lobes (*arrows*) as well as new hyperintensity in the brainstem (*double-lined arrow*) and occipital lobes (*arrowheads*). **C:** T2-weighted coronal MRI of the brain on initial presentation shows white-matter T2 signal hyperintensity throughout the cortex, with the right side greater than the left side. **D:** T2-weighted coronal MRI posterior to panel C shows T2 signal hyperintensity in the right middle cerebellar peduncle (*arrow*). **E and F:** Axial diffusion-weighted (DWI) and apparent diffusion coefficient (ADC) MRI sequences performed on the day of presentation show signal hyperintensity and hypointensity, respectively, (*arrows*) consistent with acute restricted diffusion due to infarction in the bilateral corona radiata. **G and H:** DWI and ADC show restricted diffusion in the left frontal lobe. Restricted diffusion was also seen in the left parietal lobe posteriorly (not shown). **I:** Repeat electrocardiogram on day 4 of admission, day 6 of upper respiratory symptoms, shows nonspecific amplitude changes and T-wave abnormalities most prominent in high lateral and anterior septal leads. **J and K:** Axial and coronal 3D fast imaging employing steady-state acquisition MRI of the brain on day 3 of admission shows signal hyperintensity in the olfactory tract (*arrows*). **L and M:** Axial and coronal views of the same sequence show thickening of the left vagus nerve (*arrow*).

leukoencephalopathy (CADASIL), caused by mutations in *Notch3*,[7] acutely worsened by COVID-19 infection, to better understand the relationship of preexisting cerebrovascular pathology and SARS-CoV-2 in producing ischemic stroke.

Illustrative Case

A 64-year-old male with a history of hypothyroidism and prior stable imaging findings consistent with CADASIL (Fig. 1A) presented with dysarthria after a 3-day history of flulike symptoms. Maternal family history was significant for CADASIL due to confirmed *Notch3* mutation. He was previously followed for 20 years and reported migraines but had no neurological impairment. On hospital presentation he was otherwise neurologically intact. Laboratory findings included an elevated fibrinogen, D-dimer, and positive reverse transcription–polymerase chain reaction (RT-PCR) for SARS-CoV-2 (Table 1). Diffuse symmetrical, confluent fluid-attenuated inversion recovery (FLAIR) hyperintensity in the periventricular and subcortical white matter involving the bilateral frontal lobes, bilateral temporoparietal lobes, and the pons was evident on MRI, consistent with progression of known CADASIL (Fig. 1B–D). MRI also revealed several acute infarcts (Fig. 1E–H). Magnetic resonance angiography was negative for large vessel occlusion or critical intracranial or extracranial stenosis. Pharmacotherapy included a regimen of daily aspirin, clopidogrel for 2 days, enoxaparin, a single dose of vancomycin, twice-daily cefepime, and a taper of hydroxychloroquine in conjunction with azithromycin for a total of 5 days. Three days following admission, he developed hoarseness, left-sided supranuclear facial nerve paresis, bilateral complete ophthalmoparesis, and transient finger agnosia. Electrocardiography demonstrated new T-wave abnormalities in high lateral and anteroseptal leads without elevated troponins (Fig. 1I). Repeat MRI subsequently demonstrated interval increases in the size of previously noted acute infarcts and worsening FLAIR signal in the brainstem. Hyperintensity of the olfactory tract and mild thickening of the left vagus nerve were appreciated on magnetic resonance (MR) neurography (Fig. 1J–M). On day 12 of admission, the patient was discharged to a rehabilitation facility with mildly improved dysarthria, difficulty ambulating, difficulty tracking horizontally, and expressive aphasia. Vision, olfaction, and hearing remained intact.

Discussion

Observations

This case highlights the potential tropism of SARS-CoV-2 for both neurons and vasculature.[8] The sudden dramatic progression of the patient's previously relatively benign CADASIL phenotype and the delayed onset of neurological deficits following several days of FLAIR signal throughout the brainstem suggests that these imaging findings were due to SARS-CoV-2 infection in the cerebrovasculature and brain parenchyma. Retrograde neurotropic spread of the virus to the brain via the cranial nerves (CNs) from primary sites of infection such as the nasopharynx and lung has previously been suggested.[8,9] Recent data suggest that CN involvement in the setting of COVID-19 is not rare, with CNs I, VII, IX, and X most frequently implicated in cases of intracellular neurotropic spread and often manifesting as hyposmia/anosmia, ophthalmoparesis, and hypogeusia/ageusia.[9] Multiple viruses have been associated with abnormal CN VII enhancement on MRI, including herpes simplex virus type 1, cytomegalovirus, and varicella zoster.[10] However, virus-mediated hypertrophy and enhancement of CN IX and X have only been correlated with varicella zoster.[11] The thickening of the vagus nerve and olfactory

TABLE 1. Patient clinical characteristics and laboratory findings

	Value
Clinical characteristics	
Demographics	
Age, yrs	64
Sex	Male
Past medical history	
Tobacco status	Cessation > 20 yrs ago
Hypothyroidism	
Home medications (dose and route)	
Levothyroxine	150 μg per day orally
Atorvastatin	40 mg daily orally
Laboratory investigations	
Viral screening	
SARS-CoV-2 RT-PCR	Positive
Rapid HIV screen	Negative
Complete blood count	
White blood cell count ($4.0–11.0 \times 10^3/\mu L$)	4.3
Neutrophil band count (0–6%)	0
Segmented neutrophils (60–80%)	62
Lymphocyte count (20–40%)	24
Monocyte count (2–6%)	10
Red blood cell count ($4.1–5.8 \times 10^6/\mu L$)	4.66
Hemoglobin (13–16.5 g/dL)	14.7
Coagulation studies	
Platelet count ($150–450 \times 10^3/\mu L$)	157
Prothrombin time (10.4–12.8 sec)	15.2
Activated partial thromboplastin time (25.5–36.5 sec)	31.8
Prothrombin mixing study, undiluted (10.4–12.8 sec)	15.5
Prothrombin mixing study 1:1 (10.4–12.8 sec)	13.0
Factor II assay (50–154%)	115
Factor VII assay (51–186%)	55
Factor VIII assay (60–125%)	168
Factor IX assay (60–177%)	93
Factor X assay (76–183%)	99
Factor XI assay (60–150%)	82
Factor XII assay (50–150%)	75
Liver function studies	
Albumin (3.8–4.9 g/L)	3.9
Alanine aminotransferase (7–52 U/L)	23
Aspartate aminotransferase (15–41 U/L)	33
Inflammatory markers	
Fibrinogen (210–480 g/L)	>700

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TABLE 1. Patient clinical characteristics and laboratory findings

	Value
D-Dimer (68–500 ng/mL)	847.5
Serum ferritin (15–300 ng/mL)	376.6
Lactate dehydrogenase (140–240 U/L)	168
Lipid panel	
Cholesterol (130–200 mg/dL)	121
Triglycerides (< 150)	90
HDL cholesterol (35–75 mg/dL)	26
LDL cholesterol, direct (< 100 mg/dL)	81

HDL = high-density lipoprotein; HIV = human immunodeficiency virus; LDL = low-density lipoprotein; RT-PCR = reverse transcription–polymerase chain reaction. Patient demographics, past medical history, and home medications, which were continued during the hospital course, are shown. Laboratory investigations during the hospital stay are shown.

tract enhancement by MR neurography support the hypothesis of neurotropic spread in this patient. We believe the delay in appearance of symptoms and radiological signs may be due to a latency period in which the virus replicates and disseminates via retrograde axonal transport without initial destruction.[12] The acute worsening of CADASIL, a heritable microangiopathy, by SARS-CoV-2 infection may be attributable to the expression of angiotensin-converting enzyme 2 (ACE2), which acts as the receptor for the virus, on vascular endothelium.[8,13] ACE2 is inactivated upon viral binding,[13] which may result in excessive vasoconstriction and vasospasm mediated by increased levels of angiotensin II. Notably, CADASIL has been associated with increased maximal responsiveness and decreased blunting of tachyphylaxis to the constrictor effects of angiotensin II.[14] We believe that the vasospastic insult by SARS-CoV-2 infection superimposed upon CADASIL may have acted as a nidus for the development of the acute ischemic microangiopathy observed in this patient.

Lessons

The pathophysiology of cerebrovascular ischemia in the setting of SARS-CoV-2 infection remains unclear. While risk factors for neurological sequelae of COVID-19 naturally emphasize populations with immunodeficiency or chronic inflammatory illnesses, noninflammatory heritable or acquired arteriopathies confer additional susceptibility for stroke through deficiencies in cerebral autoregulation. We present a unique case of multiple ischemic strokes in a patient with CADASIL with acute COVID-19 infection with delayed involvement of the brainstem to highlight innate mechanistic failure of cerebral autoregulation in conjunction with viral tropism for both vasculature and neurons. Further research regarding the specific mechanism of cerebrovasculature and CN infiltration for coronavirus is merited.

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Disclosures

Dr. Rosenblum is affiliated with NeuroSimplicity, LLC, which is a medical device and technology company focusing on medical image processing. No other disclosures were reported.

Author Contributions

Conception and design: Rosenblum, Tunacao, Dang, Downing, Zhuang. Acquisition of data: Rosenblum, Tunacao, Badia, White. Analysis and interpretation of data: Rosenblum, Tunacao, Nazari, Bluestone, Badia. Drafting of the article: Rosenblum, Tunacao, Nazari, Dang, Smirniotopoulos. Critically revising the article: Rosenblum, Tunacao, Nazari, Ronk, Dang, Zhuang, Heiss, White. Reviewed submitted version of manuscript: Rosenblum, Tunacao, Ronk, Zhuang, Heiss. Approved the final version of the manuscript on behalf of all authors: Rosenblum. Administrative/technical/material support: Dang, Zhuang, Badia. Study supervision: Rosenblum.

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