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.

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Letter to the Editor

Ischemic stroke associated with aneurysmal lenticulostriate vasculopathy and symmetric reversible basal ganglia lesions in COVID-19

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Dear editor

An association between stroke and COVID-19 has been reported in a number of cohorts. The mechanisms underlying this assocation remain uncertain, but hypercoagulability related to a diffuse inflammatory response has been postulated as an important factor. Vasculitis has also been proposed as a potential stroke mechanism, though evidence of central nervous system vasculitis in adults is, to date, limited. [1,2] We report the case of a young, healthy man with acute COVID-19 causing minimal systemic symptoms but leading to a highly unusual pattern of bilateral cerebral infarctions, transient symmetric hyperintensity of the basal ganglia on MRI FLAIR sequences, and bilateral aneurysmal lenticulostriate vasculopathy. This case raises important questions about vascular involvement in the setting of COVID-19.

A 24-year-old man without significant past medical history presented with left hemiparesis. The evening before presentation, he noted abrupt onset mild dysarthria and left leg weakness that impaired walking. He did not initially seek medical attention, but the next morning awoke with left face and arm weakness and called for an ambulance. On hospital arrival, he was afebrile with normal vital signs and oxygen saturation. Examination showed mild left hemiparesis; the NIH Stroke Scale score was 3. Nasopharyngeal swab PCR testing for SARS-CoV-2 was positive. On further questioning after this result, he reported a mild sore throat that started two weeks prior, and had noted some loss of taste and smell, but denied any respiratory symptoms. Initial brain CT/CT angiography of head and neck showed left caudate hypodensity of indeterminate age, and multiple areas of beading along the lenticulostriate vessels bilaterally, likely representing multifocal aneurysmal dilatations (Fig. 1, panel A). Brain MRI demonstrated multifocal acute/subacute subcortical infarctions, symmetric bilateral hyperintense signal involving the deep gray structures (Fig. 1, panel B-F), and beaded enhancement along the lenticulostriate vessels concordant with the CTA. Extensive additional diagnostic testing was unrevealing, including sedimentation rate, C-reactive protein, D-dimer, ferritin, PT/PTT, lipid panel, RPR, hepatitis panel, and hypercoagulable and rheumatologic testing. Lumbar puncture was performed and cerebrospinal fluid was unremarkable (1 white blood cell, normal protein and glucose). CSF testing for cryptococcus, VZV, HSV, CMV, EBV, AFB, and toxoplasmosis was negative. Transthoracic echocardiography did not reveal a cardiac source of embolus.

He was started on daily aspirin and, given suspicion for an inflammatory process on the MRI, prednisone 60 mg daily and discharged home. On follow-up one month later, he felt neurologically back to baseline, with complete resolution of his deficits. Formal examination showed only trace left leg weakness. He was tapered off steroids and MRI was repeated at 3 months (Fig. 1, panel G-I). This showed resolution of the hyperintense signal in the basal ganglia and near-complete resolution of the lenticulostriate vascular beading. At follow-up 4 months later, he was well with no recurrent or ongoing symptoms.

Most patients with stroke associated with COVID-19 are older with traditional vascular risk factors and often critically ill, suggesting SARS-CoV-2 infection is rarely the sole factor precipitating stroke. However, reports of stroke in otherwise healthy young patients with COVID-19 suggest novel mechanisms may be operative in some cases. Endothelial dysfunction resulting specifically from SARS-CoV-2 infection has been postulated. A Kawasaki-disease like vasculitic syndrome (multisystem inflammatory syndrome in children, MIS-C) associated with COVID-19 has been observed in children, and a post-infectious cerebral arteritis has been reported in two children. [3,4] At least two cases of purported CNS vasculitis causing stroke in adults with COVID-19 have been reported, both with severe respiratory dysfunction. [1,2] In neither case was pathology obtained. In one, vessel imaging was normal and vasculitis was proposed based on the pattern of infarction; in the other the diagnosis of vasculitis was based on MRI vessel wall imaging showing concentric enhancement.

Our patient never had significant systemic illness related to COVID-19, nor was there elevation of systemic inflammatory markers. The transient bilateral basal ganglia abnormalities raised concern for an inflammatory process – whether resolution was spontaneous or related to treatment with steroids is impossible to determine in this single case. Similar transient basal ganglia abnormalities may be seen with metabolic derangements, though no such specific abnormalities in laboratory testing were present in this case. The observed aneurysmal lenticulostriate vasculopathy also raised concern for an inflammatory process,

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although non-inflammatory vascular mechanisms could not be excluded. Reversible cerebral vasoconstriction syndrome, a non-inflammatory vasculopathy modulated by dysregulation of vascular tone, and the vasculopathy seen with rare diseases associated with elevated vascular endothelial growth factor [5], provide examples of vascular pathologies leading to structural arterial changes independent of inflammation. It is possible that binding of SARS-CoV-2 to the angiotensin-converting enzyme 2 receptor with subsequent disruption of the renin-angiotensin system might lead to a similar phenomenon affecting the vasculature.

It should be noted that the combination of radiographic findings seen in this case is extraordinarily unusual, and the temporal association with characteristic, albeit mild, COVID-19 illness strongly suggests a true association with SARS-CoV-2 infection in this patient. Vessel findings

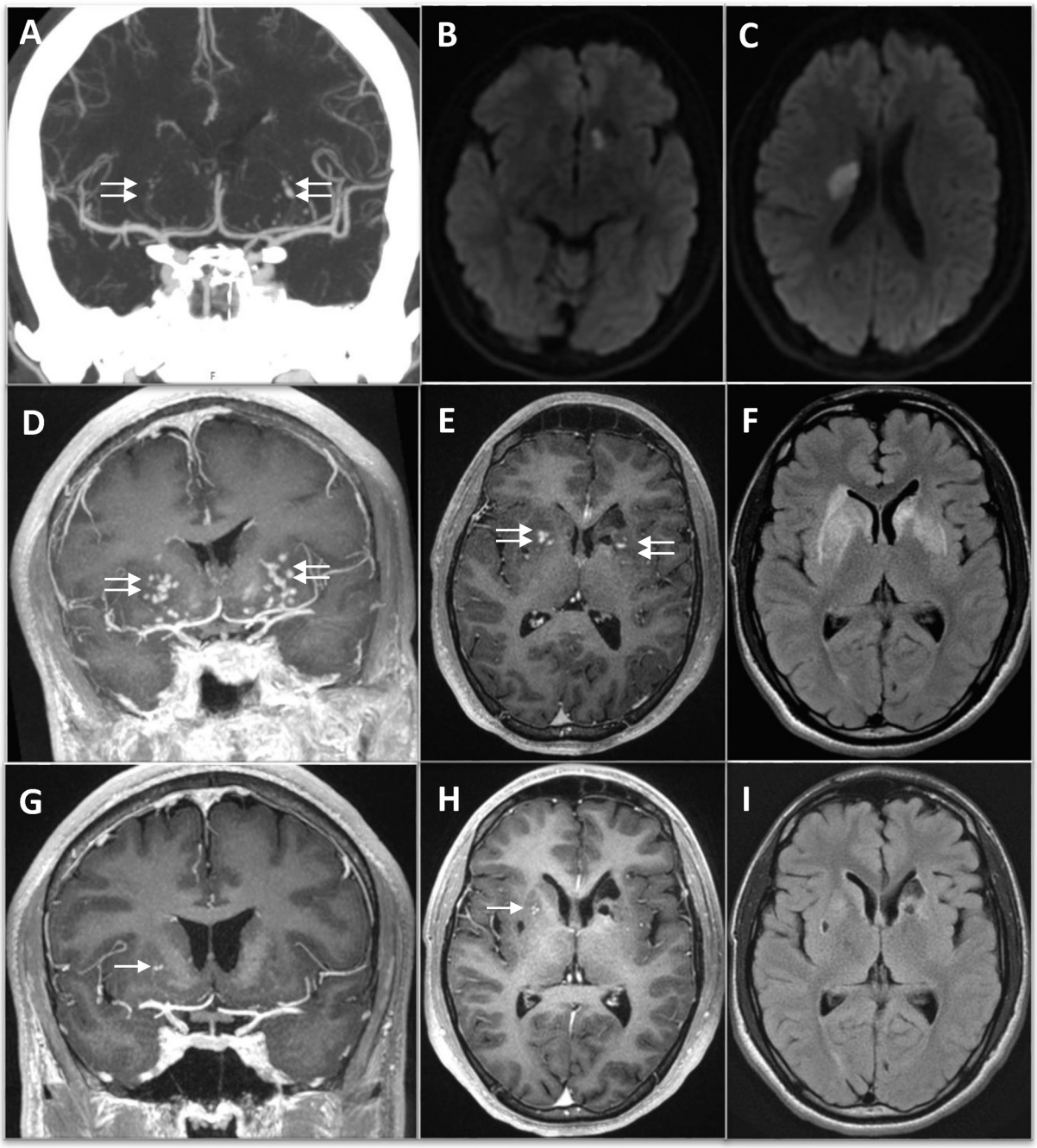

Fig. 1. CT angiography and MRI showing cerebral infarction, lenticulostriate vasculopathy, and basal ganglia lesions in patient with COVID-19.
Figure legend: Initial CTA (coronal MIP) (A) reveals multiple areas of beading along the lenticulostriate vessels bilaterally, likely representing multifocal aneurysmal dilatations (arrows). MRI DWI images (B & C) show diffusion restriction in the inferior portion of the left caudate head and right corona radiata consistent with multifocal infarcts. Similar to CTA, initial contrast-enhanced T1W coronal and axial MR images (D & E) depict a beaded lenticulostriate enhancement pattern. Axial FLAIR images (F) show near-symmetric areas of hyperintense signal and swelling involving the deep gray structures bilaterally (including the caudate nuclei, putamina, internal capsules, globus pallidi and extreme capsules). Notably, the thalami are spared. There is no diffusion restriction or hemorrhage corresponding to these regions (images not shown). On follow-up imaging 3 months later, coronal and axial contrast-enhanced T1W MR images (G & H) show near-complete resolution of beaded enhancement with minimal residual beading in the right putamen (arrows). Additionally, there is resolution of abnormal hyperintense signal on axial FLAIR images (I), with expected evolution of infarcts in the right putamen, left caudate nucleus and internal capsule.

similar to those we observed have been reported in one case prior to the COVID era, in which they were ascribed to possible primary angiitis of the central nervous system. [6] As experience with the clinical spectrum of COVID-19 expands, a more detailed view of the interaction between SARS-CoV-2 and the cerebral vasculature will hopefully emerge.

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