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NEURO-IMAGES

# COVID-19-Associated Acute Multi-infarct Encephalopathy in an Asymptomatic CADASIL Patient

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COVID-19 is a new disease caused by the SARS-CoV-2 virus. First described in Wuhan, China, the scope and speed with which the disease has spread has placed healthcare systems around the world under pressure. Afflicted patients typically present with fever, cough, myalgia, and eventually dyspnea. Despite the characteristic presentation of COVID-19, we have frequently noted atypical symptoms including gastrointestinal disturbances and neurological symptoms including headache, altered mental status, loss of olfaction, and seizures. We present the case of a patient who presented with significant neurological symptoms.

A right-handed female in her early 40s presented to the emergency department after she developed dysphagia, dysarthria, and encephalopathy 2 days prior to admission. She had a history of well-controlled hypertension and dyslipidemia. The patient had no past medical history of stroke, migraines, visual disturbances, or any neurological disease processes. She had no previous brain imaging studies. There was also no family history of stroke, dementia, migraines with aura, or other neurological disorders.

Eleven days prior to admission, the patient began suffering from a headache and myalgia. She was seen by her primary care physician and treated as an outpatient with a course of azithromycin. She had a negative influenza swab and a negative rapid strep test at the office. She was, however, not checked for COVID-19 due to the lack of available testing. The patient's sister, with whom she resided, had recently returned from a trip abroad. The day after returning, the sister developed a headache and myalgias which were mild, lasted 4 days, and were self-limited. Her sister did not seek any medical care. The patient fell ill 4 days after her sister's return with similar symptoms of a headache and myalgias. After developing lethargy, dysphagia, and speech difficulties, she was brought to the emergency department.

The physical examination revealed a patient in moderate acute distress. She was febrile with a temperature of 102.2°F. Her blood pressure was 140/80 with a heart rate of 106 and a respiratory rate of 27. The room air oxygen saturation was 92%. Neurologically, she was awake and alert and followed commands although sluggishly. She had difficulty with her speech with components of both dysarthria and expressive aphasia, difficulty handling her secretions, and dysphagia. There was no meningismus which could be elicited. Her pupils were equal round and reactive, but she showed a right gaze preference and a mild left facial droop. She had mildly decreased but equal bilateral strength. The deep tendon reflexes were preserved. The remainder of the examination was only notable for diffuse rhonchi on auscultation of her lungs.

Initial laboratory studies showed a mild leukocytosis with lymphopenia. The chest X-ray demonstrated patchy consolidation in the right lower lung. A non-contrast computed tomography (CT) of the head showed no evidence of intracranial hemorrhage, but there were multifocal patchy areas of white matter hypoattenuation (Fig. 1). A lumbar puncture was performed to clarify the diagnosis and to exclude central nervous system infection. Cerebrospinal fluid (CSF) analysis revealed normal cell counts, protein, and glucose. A polymerase chain reaction (PCR) panel for meningitis and encephalitis, including herpes simplex 1 and 2, human herpes 6, Cryptococcus, and Varicella Zoster virus, was entirely negative as were bacterial cultures. A Lyme titer was negative.

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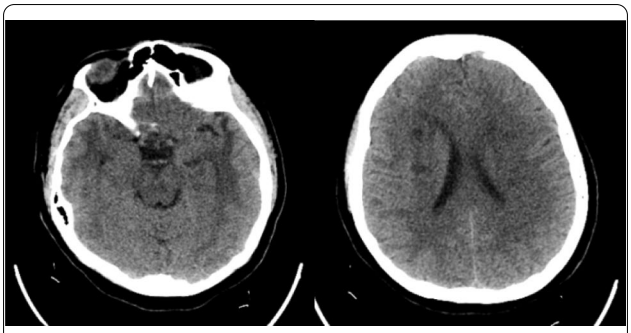

**Fig. 1** CT head—bilateral temporal and subcortical hypodensity

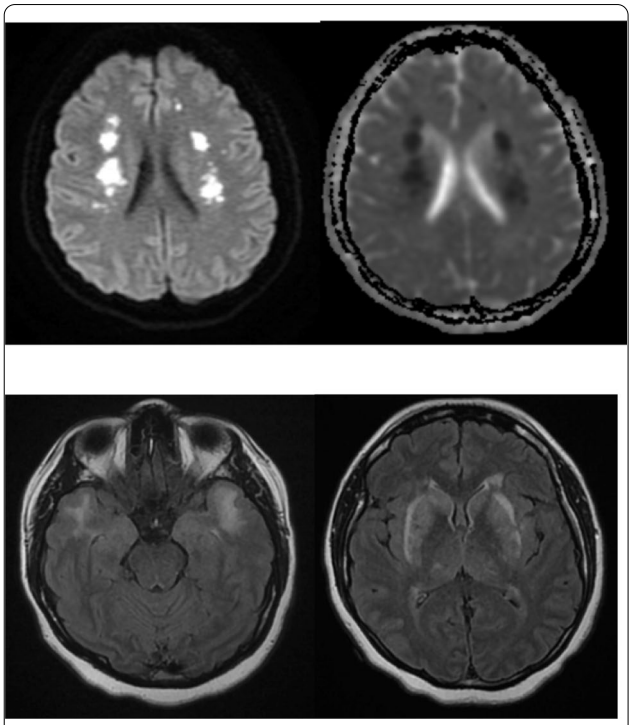

**Fig. 2** (Top) MRI brain (Top, Left)—subcortical diffusion-weighted imaging (DWI), and (Top, Right) apparent diffusion coefficient (ADC) map changes. (Below) MRI brain—subcortical and temporal T2 FLAIR changes

An electroencephalogram (EEG) did not show electrical evidence of seizures. The COVID-19 PCR test of a nasal swab became available 2 days after admission and detected the novel coronavirus (SARS-CoV-2) target nucleic acid. The COVID-19 PCR test of CSF was negative (Cepheid GeneXpert System).

To assess the white matter lesions found on head CT, a magnetic resonance imaging (MRI) of the brain with and without contrast was obtained. The MRI showed extensive patchy areas of abnormal signal involving bilateral frontoparietal white matter, anterior temporal lobes, basal ganglia, external capsules, and thalami. Additionally, some of these foci demonstrated diffusion-weighted imaging (DWI) changes and corresponding apparent diffusion coefficient (ADC) changes, with questionable minimal enhancement (Fig. 2). Magnetic resonance angiography (MRA) of the brain and neck was essentially normal.

The patient was treated with hydroxychloroquine, ceftriaxone, and a 5-day course of intravenous immunoglobulins (IVIG). Steroids were not used as it was felt to be contraindicated given the acute COVID-19 diagnosis and in keeping with the then current guidelines. The patient was also given aspirin for stroke prophylaxis. After 5 days of IVIG, the patient showed signs of improvement—she was better able to handle secretions, less dysarthric, afebrile and had no respiratory symptoms. Because of her acute COVID-19 diagnosis, it was difficult to get her placed in a rehabilitation facility. The patient's speech, strength, and ability to swallow continued to improve, and she was able to be discharged to home by hospital day 23. At an outpatient follow-up 1 week after discharge, the patient was found to be almost at baseline—tolerating a regular diet, normal speech, symmetric face, normal motor and sensory examination, and able to ambulate independently albeit at a slow pace, with some easy fatigability.

A follow-up brain MRI (Fig. 3) was performed 7 weeks after the initial MRI study. It showed that the initial DWI and ADC changes had largely disappeared. There was a hypodense area on T1 FLAIR images without enhancement and with persistent T2 FLAIR changes in a similar distribution as previous MRI. The chronological changes from the initial DWI and ADC images to the disappearance of these signals in the follow-up MRI support that the patient had acute subcortical ischemic changes or necrotic changes. The patient continued to recover from her acute illness, and 8 weeks post-discharge she resumed driving and returned to her previous work.

An additional workup became available a month after the second MRI including a negative myelin antibody and NOTCH 3 genetic testing. It revealed the presence of a pathogenic variant in the NOTCH3 gene—a heterozygous missense mutation (Sequencing Test by Athena Diagnostics) which was consistent with a diagnosis of CADASIL.

It is important to consider other infectious etiologies with or without a diagnosis of COVID-19 in a patient with fever, neurological deficits, and encephalopathy. An electroencephalogram (EEG) is indicated to exclude subclinical seizures and non-convulsive status epilepticus. The CT findings prompted a further workup for cerebral abscesses and septic emboli. It is difficult to perform an MRI on a COVID-19-positive patient or a person under

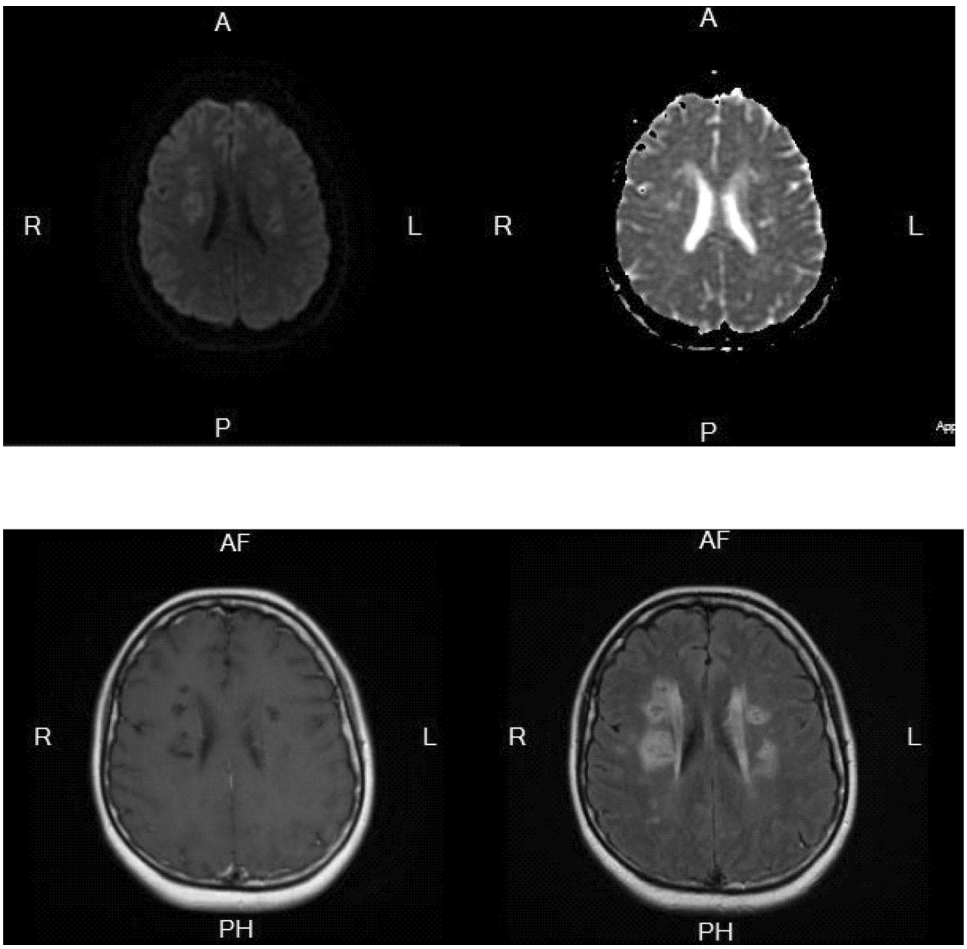


**Fig. 3** Follow-up MRI brain of this patient 7 weeks later. (Top, Left) MRI brain—subcortical diffusion-weighted imaging (DWI) with only slight bright signal, (Top, Right) apparent diffusion coefficient (ADC) map with normal signal. (Below, Left) MRI brain—T1 FLAIR with contrast—subcortical hypodensity areas without enhancement, and (Below, Right) T2 FLAIR with contrast with increased signal changes

investigation (PUI) due to the concern for contamination of equipment, the requisite patient transportation, and the risk of exposure to healthcare providers. Given the clinical picture and the CT findings, it seemed rational to take the necessary steps to obtain such imaging. The brain MRI showed multiple DWI lesions and corresponding ADC sequence changes which were consistent with multiple acute infarcts possibly related to hypoxic–ischemic injury from systemic perturbations and resultant tissue hypoxia. The predominance of the extensive T2 FLAIR signal changes in the cerebral white matter lesions is more suggestive of a demyelinating process. These lesions are extensive, bilateral, and predominantly subcortical, with additional involvement of the deep nuclei. These features are compatible with an acute inflammatory encephalopathy in the setting of a recent or ongoing systemic viral infection with acute neurological deficits. This case potentially represents atypical acute disseminated encephalomyelitis (ADEM) as the CSF did not show any pleocytosis or increased protein levels [1], though absence of CSF changes could be related to the timing of lumbar puncture. The initial presentation of multiple sclerosis is within the differential diagnosis, but given the lack of any prior neurological symptoms and the clinical picture described as well as the acute diagnosis of COVID-19 it seems unlikely. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated encephalitis is also a consideration; however, the patient had negative myelin antibody. In a patient with multiple infarcts, the differential diagnosis also includes a cardioembolic cause. In this case, it was initially suspected that these multiple infarcts could be from a combination of hypoxia and a hypercoagulable state from the acute COVID-19 infection [2].

The subcortical multiple infarcts this patient experienced along with the relatively symmetric white matter lesions seen on brain MRI suggest a case of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The acute infection combined with a complete lack of family history of stroke, dementia or migraine, and the patient lacking of prior migraine with aura, stroke, cognitive impairment, or psychiatric illness is unusual but does not exclude a diagnosis of CADASIL as de novo cases have been described. The clinical course of complete recovery in a few weeks is also atypical for a diagnosis of CADASIL. Our patient did undergo genetic testing which revealed the presence of a pathogenic variant in the NOTCH3 gene consistent with CADASIL.

It is still not clear if the multiple subcortical infarctions seen on MRIs are from CADASIL itself, or some combination of direct viral invasion, an immunological reaction, or a cytokine storm syndrome despite the findings of normal CSF and a negative COVID-19 PCR of the CSF. The distribution of the CT and MRI changes in our case is similar to a recent case report of acute hemorrhagic necrotizing encephalopathy in a COVID-19 patient [3], which case, to our knowledge, was not tested for a pathological NOTCH3 mutation.

We present a unique case of acute multi-infarct encephalopathy in a COVID-19 patient. The clinical features and CT and MRI changes are consistent with acute subcortical multiple infarctions which could be related to or provoked by a viral infection. Further genetic testing revealed this previously asymptomatic patient to have a pathogenic variant of the NOTCH3 gene consistent with CADASIL. Even though it is known that there are vascular wall smooth muscle abnormalities related to CADASIL gene mutations, it is not clear what triggers the multiple infarcts in these patients. The acute infection likely induced a milieu of inflammation, hypoxia, and coagulopathy in this COVID-19 patient which triggered multiple infarcts. Further investigation as to the precipitants of the hypoxic–ischemic process in CADASIL patients is of interest.

Our described case is an atypical presentation of an acute COVID-19 infection in a previously asymptomatic CADASIL patient who presented with multiple infarcts and encephalopathy. It is illustrative of the difficulty in searching for a definite diagnosis and the requisite workup to explore the different treatable etiologies of this clinical picture.

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**Author Contributions**
All authors participated in the clinical work. T. Zhang and M.B. Rodricks wrote the draft.

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**Conflict of interest**
The authors declare that they have no conflict of interest.

**Ethical Approval/Informed Consent**
IRB approval was obtained for this study.

## Publisher's Note



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