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CASE REPORT **OLGU SUNUMU**

MULTIPLE CEREBRAL INFARCTS TRIGGERED BY SARS-COV-2 VIRUS IN AN ASYMPTOMATIC CADASIL PATIENT: CASE REPORT

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ABSTRACT

During the coronavirus pandemic, increasing evidence has confirmed that the SARS-CoV-2 virus is susceptible to increased risk of stroke. On the other hand, the relationship between the SARS-CoV-2 virus and CADASIL was among the topics discussed in the literature with a small number of cases. In this case report, we present multiple cerebral infarcts in an asymptomatic CADASIL patient and we aim to shed light on the complex nature of cerebrovascular manifestations of the SARS-CoV-2 virus. A 50-year-old man with an unremarkable past medical history was admitted to our department with fever and neurologic manifestations on the 6th day of self-isolation due to positive reverse-transcriptase–polymerase-chain-reaction assay in a nasopharyngeal sample for SARS-CoV-2. Neurological deficits were related to the acute vascular lesions located in the border-zone areas of both hemispheres, corpus callosum, and cerebellar peduncles on brain MRI. Lesions in chronic nature in the bilateral subcortical white matter predominantly involving the external capsule and temporal poles were also challenging. As a result of a comprehensive study that could explain the neurological status and imaging findings, the CADASIL diagnosis is reached by genetic testing for NOTCH-3. The experience, in this case, suggests considering patients with suspicious MRI findings for CADASIL diagnosis during the coronavirus pandemic. Further studies are needed to explain the underlying pathophysiological mechanisms related to cerebrovascular manifestations of SARS-CoV-2.
Keywords: SARS-CoV-2, CADASIL, NOTCH-3, stroke.

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ASEMPTOMATİK CADASIL HASTASINDA SARS-COV-2 VİRÜSÜ TARAFINDAN TETİKLENEN MULTİPL SEREBRAL ENFARKTLAR: OLGU SUNUMU

ÖZ

Koronavirüs pandemisi süresince artan kanıtlar SARS-CoV-2 virüsünün artan inme riskinden sorumlu olduğunu doğruladı. Öte yandan SARS-CoV-2 virüsü ile CADASIL arasındaki ilişki az sayıda vaka ile literatürde tartışılan konular arasında yer aldı. Bu olgu sunumunda, asemptomatik bir CADASIL hastasında izlenen multipl serebral enfarktları sunuyoruz ve SARS-CoV-2 virüsünün serebrovasküler belirtilerinin karmaşık doğasına ışık tutmayı amaçlıyoruz. Özgeçmişinde özellik olmayan 50 yaşındaki erkek hasta. SARS-CoV-2 için alınan nazofarengial numunesinin pozitif polimeraz zincir reaksiyonu testi nedeniyle izolasyonunun 6. gününde ortaya çıkan ateş ve nörolojik belirtileriyle kliniğimize başvurdu. Nörolojik belirtileri beyin MRG'da her iki hemisferin sınır sulama alanlarında, korpus kallozum ve serebellar pedinküllerde yer alan akut vasküler lezyonlarla ilişkiliydi. Ağırlıklı olarak eksternal kapsül ve temporal kutupları içeren iki yanlı subkortikal beyaz cevherde yer alan kronik doğadaki lezyonları dikkat çekiciydi. Nörolojik tablosunu ve görüntüleme bulgularını açıklayabilecek kapsamlı bir çalışma sonucunda, NOTCH-3 için genetik test yapılarak CADASIL teşhisine ulaşıldı. Bu olgudaki deneyim, koronavirüs pandemisi sırasında şüpheli MRG bulguları olan hastalarda CADASIL tanısını göz önünde bulundurmayı telkin etmektedir. SARS-CoV-2'nin serebrovasküler belirtileriyle ilgili altta yatan patofizyolojik mekanizmaları açıklamak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: SARS-CoV-2, CADASİL, NOTCH-3, inme.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak in Wuhan city, China, spread rapidly throughout China and gradually to all countries worldwide as a global pandemic. The primary manifestation of the disease due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) is respiratory and cardiac symptoms. However, considerable neurological manifestations are also reported in the literature as case reports, case series, and in nationwide observational studies recently (1-3).

As the infection is known to be a trigger for stroke, there is increasing emerging evidence supporting the association between the SARS-CoV-2 virus and stroke in individuals with genetic predisposition or depending on other vascular factors. But the etiopathogenesis, extent of the risk and, stroke characteristics are still unclear and under investigation (4). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is one of the most common hereditary cerebral small vessel diseases caused by mutations in NOTCH3 characterized by a variable combination of migraine, recurrent cerebral infarction, transient ischemic attacks, epilepsy, progressive white matter degeneration, psychiatric disturbances, and finally vascular dementia (5,6). To date, SARS-CoV-2 virus-induced stroke in CADASIL patients is limited to a few case reports (7-10).

Herein, we present a case of multiple cerebral infarcts in an asymptomatic CADASIL patient with a heterozygous pathogenic NOTCH3 variant and aim to shed light on the complex nature of cerebrovascular manifestations of the SARS-CoV-2 virus.

CASE REPORT

A 50-year-old right-handed man presented with high fever and epileptic seizure on the 6th day of self-isolation due to a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay in a nasopharyngeal sample for SARS-CoV-2. But shortly after his seizure, he developed acute speech, and gait disturbances, and was hospitalized. During his neurological examination on admission, he was partially oriented to place and time. Slurred speech, ataxia of the limbs, and trunk were noted with exaggerated deep tendon reflexes and bilaterally positive Babinski sign. He had no significant previous medical history. But his father had a past medical history of stroke in his early 60s and he was immobile due to stroke sequelae before he died.

Blood test results showed a white blood cell count of $8.15x10^3$/uL, lymphocytes $1.62x10^3$/uL, C-reactive protein 116.8 mg/L, ferritin of 413.9 ug/L, and D-dimer of 981 ug/L. Other investigations such as prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and liver

enzymes were all normal. A computed tomography (CT) scan of the patient's chest showed ground-glass opacity suggestive of viral pneumonia. Brain magnetic resonance imaging (MRI) was performed to assess the neurological status. Diffusion-weighted images showed multiple high-signal-intensity lesions in the border-zone areas of both hemispheres, corpus callosum, and cerebellar peduncles suggesting acute infarcts (Figure 1). MRI fluid-attenuated inversion-recovery (FLAIR) showed high-intensity signal changes in the bilateral subcortical white matter predominantly involving the external capsule and temporal poles (Figure 2).

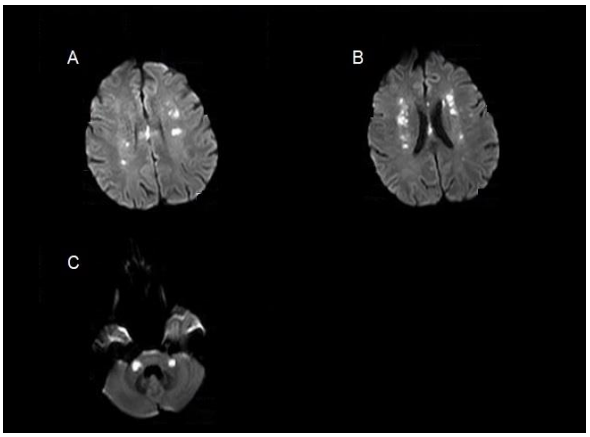

Figure 1. Diffusion-weighted images showed multiple high-signal-intensity lesions in the border-zone areas of both hemispheres, corpus callosum (1A and 1B), and cerebellar peduncles (1C) suggesting acute infarcts.

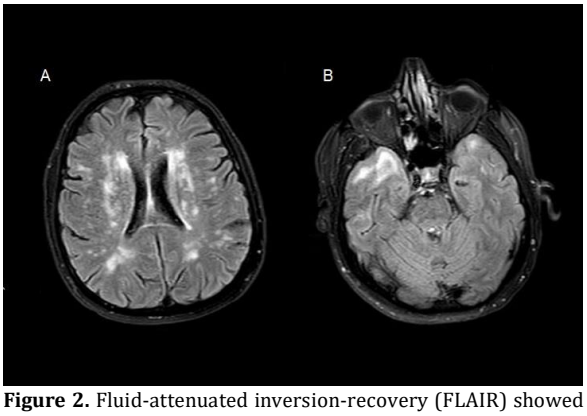

Figure 2. Fluid-attenuated inversion-recovery (FLAIR) showed high-intensity signal changes in the bilateral subcortical white matter predominantly involving the external capsule (2A) and temporal poles (2B).

No contrast enhancement was noted on T1-weighted images. Both CT-angiography and the following digital subtraction angiography revealed normal cerebral vasculature. Baseline ECG, 24-hour holter monitoring, and cardiac imaging with echocardiography were all normal. Serology for HIV, hepatitis B, C, and syphilis was negative. An extensive workup for vasculitis excluded any other causative autoimmune pathology. A lumbar puncture was performed and revealed clear cerebrospinal fluid (CSF) with 3 leukocytes/mm, no glucose depletion, and a protein concentration of 65.8 mg/dL. CSF testing for the SARS-CoV-2 virus could not be performed, but CSF culture showed no bacterial growth, and tests for herpes simplex virus 1, 2, varicella-zoster virus, and cytomegalovirus were all negative. Oligoclonal bands were not present. During clinical follow-up, improvement was seen in speech, limb coordination, and trunk stability with the combination of anticoagulant and antiplatelet therapy, prompt hydration, and antiepileptic medication for seizure control. He was discharged home on dual antiplatelet therapy and levetiracetam 500 mg twice daily. As the laboratory findings and family history were suggestive of CADASIL, a genetic test was performed and revealed a heterozygous pathogenic variant NOTCH3 (NM 000435.3): c.619C>T. Three months after hospital discharge, a neuropsychological assessment was performed and revealed ongoing abnormalities in attention and executive functioning. Impairments in verbal and visual memory were also noted. Informed consent was signed by the patient for this report.

DISCUSSION AND CONCLUSION

CADASIL diagnosis in our patient was suggested by multiple acute phase border-zone infarcts with diffuse subcortical white matter lesions predominantly involving the external capsule and temporal poles on brain MRI and past medical history of his father. The patient's previous medical history was unremarkable for diagnosis of the disease, but it is known that there may be symptomatic heterogeneity of the disease even between family members carrying the same mutation (5).

Multiple possible mechanisms associate the SARS-CoV-2 virus with ischemic stroke. Proposed mechanisms in this setting include inflammation and cytokine release, inflammation-induced coagulopathy, platelet activation and aggregation,

impaired endothelial function due to direct viral invasion that may precipitate further inflammation, cardioembolism due to cardiac injury, dehydration-induced thrombosis, and inadequate cerebral perfusion. Pre-existing vascular risk factors are also additional drivers of strokes in patients with COVID-19 (4,11). In our patient, even the mutation itself and its location may have specific predisposing features with its effects on protein function and vascular homeostasis. We did not perform a CSF test for the SARS-CoV-2 virus, so we don't have evidence of the direct invasion of the SARS-CoV-2 virus.

It is not possible to prove if the acute infarctions seen on the MRI of the patient are from CADASIL itself or related to COVID-19. But, in a patient with no remarkable past medical history and known familial inheritance of CADASIL; the temporal relation of the stroke and COVID-19 infection is quite significant for possible para-infectious processes. With the spread of COVID-19, such neurological manifestations may be mere coincidence rather than SARS-CoV-2 being a trigger agent which is difficult to conclude in a single case report. However, we attach importance to the increase of similar experiences in the literature to establish the clear association between these two entities. According to our knowledge, this is the third report suggesting the SARS-CoV-2 virus may be the trigger of multiple cerebral infarcts in an asymptomatic CADASIL patient. MRI findings in our case are very similar to the MRI findings of the recent case reports of asymptomatic CADASIL patients with COVID-19 (9,10).

In conclusion, there is a great heterogeneity from host characteristics to the extent and severity of the infectious process, which all together determine the stroke characteristics and the underlying pathophysiological mechanisms regarding the SARS-CoV-2 related stroke. Further studies are needed to explain the underlying pathophysiological mechanisms of SARS-CoV-2 to analyze the risk factors and optimal strategies for primary and secondary care of stroke in neurology practice.

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Ethics

Informed Consent: The authors declared that informed consent form was signed by the patient.

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