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【 CASE REPORT 】

Bilateral Middle Cerebellar Peduncle Sign in a Patient with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy and Coronavirus Disease 2019

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Abstract:

A 59-year-old man without risk factors for atherosclerosis was diagnosed with coronavirus disease 2019 (COVID-19). Four days later, he developed dysarthria and gait disturbance. Neurological examination revealed slurred speech, ataxia, and mild cognitive decline. Brain magnetic resonance imaging revealed multiple infarcts in the bilateral middle cerebellar peduncles and leukoencephalopathy, indicating the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Genetic testing confirmed a pathogenic *NOTCH3* variant (c.505C>T, p.Arg169Cys) (NM_000435.3). A skin biopsy supported the diagnosis. He was treated with cilostazol and after three months of rehabilitation, he regained an independent walking ability. COVID-19 increases the risk of ischemic stroke in CADASIL patients, with bilateral middle cerebellar peduncle infarctions being notable in the present case.

Key words: COVID-19, CADASIL, cerebral infarction, middle cerebellar peduncle

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Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), has been associated with various neurological disorders, including Guillain-Barré syndrome, encephalitis, and cerebrovascular diseases (1). Recently, there has been an increase in cases where patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) develop acute cerebral infarction following COVID-19 (2-10).

We herein report a patient with CADASIL who developed acute cerebral infarction, including the bilateral middle cerebellar peduncles (MCPs), after COVID-19 infection.

Case Report

The patient is a 59-year-old man with no history of migraine or risk factors for atherosclerosis. He developed a fever and sore throat but did not exhibit any respiratory symptoms. Shortly thereafter, the patient was diagnosed with COVID-19. Four days after his COVID-19 diagnosis, he experienced dysarthria, which progressively worsened over the next few days. Four days after the onset of dysarthria, he developed gait disturbance. The patient was then referred to our hospital for further evaluation.

Neurological examination revealed dysarthria, ataxia in the trunk and limbs, and mild cognitive decline. He had no history of migraines. His Mini-Mental State Examination score was 24 out of 30, and his Frontal Assessment Battery score was 9 out of 18. The Wechsler Adult Intelligence

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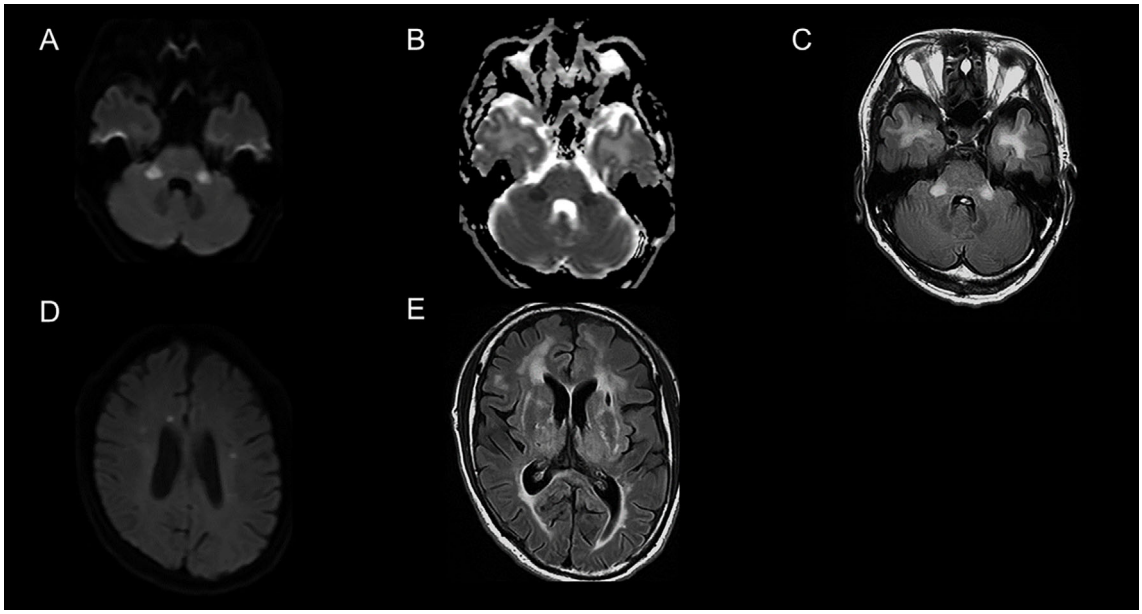

Figure 1. Brain magnetic resonance imaging (MRI) findings of the present case. Brain MRI performed when the patient developed gait disturbance showed bilateral middle cerebellar peduncle hyperintensity on diffusion-weighted images (A) with a reduced apparent diffusion coefficient (B), consistent with acute infarction. These lesions were also hyperintense on fluid-attenuated inversion recovery (FLAIR) images, and scattered acute multifocal ischemic lesions were observed in the cerebral white matter (D). Furthermore, widespread hyperintensities were observed on FLAIR images in the cerebral white matter, including the external capsule, frontal white matter (E), and temporal poles (C).

Scale Fourth Edition showed a full-scale IQ of 70, with subtest scores of 92 for verbal comprehension, 75 for perceptual reasoning, 79 for working memory, and 54 for processing speed.

Routine blood test results were unremarkable. The D-dimer levels were not increased. Tests for antinuclear antibodies, antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies were negative. Cerebrospinal fluid examination showed a cell count of 1/μL and a mildly elevated protein level of 54 mg/dL. Brain magnetic resonance imaging (MRI) showed multiple infarcts, including bilateral MCPs, on diffusion-weighted imaging. In addition, widespread hyperintensities were observed on fluid-attenuated inversion recovery (FLAIR) images in the cerebral white matter, including the external capsule, frontal white matter, and temporal poles (Fig. 1). Magnetic resonance angiography and carotid ultrasonography revealed no signs of stenosis. A Holter electrocardiogram did not detect any arrhythmia.

The presence of multiple subcortical infarcts, including those in the temporal poles, suggests the diagnosis of CADASIL. Genetic analysis of *NOTCH3* identified a heterozygous c.505C>T (p.Arg169Cys) variant (NM_000435.3), which is classified as pathogenic in ClinVar. A skin biopsy showed granular osmiophilic materials within the basement membrane of the vascular smooth muscle cells (Fig. 2). These results confirmed the diagnosis of CADASIL.

After three months of antiplatelet therapy and rehabilitation, the patient's symptoms improved. He became able to walk without assistance and was discharged.

Discussion

COVID-19 has been associated with cerebrovascular diseases, including acute ischemic stroke (1). Furthermore, it has been observed to increase the risk of acute ischemic stroke in patients with CADASIL (Table) (2-10). In these cases, COVID-19 was generally mild. Notably, 6 of 11 patients were diagnosed with CADASIL for the first time following the development of acute cerebral infarction.

The increased risk of acute ischemic stroke in patients with CADASIL may be attributable to microvascular thrombosis. This thrombosis can result from SARS-CoV-2 invading endothelial and smooth muscle cells via the angiotensin-converting enzyme 2 receptor, leading to endothelial dysfunction and subsequent vascular injury (2, 11, 12). In addition, COVID-19 can disrupt the renin-angiotensin system, causing hypoperfusion and dysregulation of cerebral blood flow. These changes increase the vulnerability of watershed regions in the brain (2, 13).

In the present case, infarction in the bilateral MCPs was a characteristic finding. Typically, bilateral MCP lesions result from conditions such as multiple system atrophy, osmotic demyelination syndrome, Wernicke's encephalopathy, posterior reversible encephalopathy syndrome, adrenoleukodystrophy, and fragile X-associated tremor/ataxia syndrome. Bilateral MCP infarction is rare in CADASIL (14). However, two

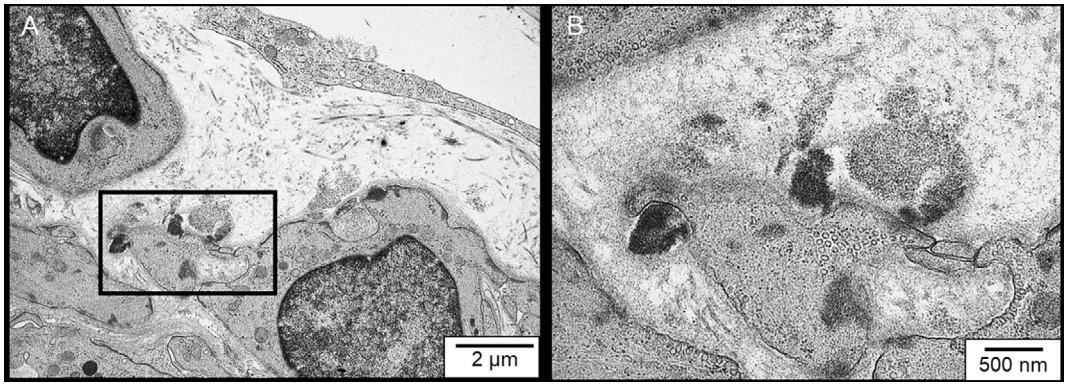

Figure 2. **In the skin biopsy, granular osmiophilic materials were observed within the basement membrane of vascular smooth muscle cells. Scale bar=2 μm (A). A higher-magnification image of the rectangular area in A is provided with a scale bar=500 nm (B).**

Table. **COVID-19-related Acute Ischemic Stroke in Patients with CADASIL.**

No.	Age	Sex	Onset after COVID-19	Diagnosis of CADASIL	DWI hyperintensities	Variant in *NOTCH3*	References
1	38	F	7 days	After COVID-19	Bilateral centrum semiovale and corona radiata	p.Arg90Cys	(2)
2	37	F	Asymptomatic	Before COVID-19	Right pons	p.Tyr1021Cys	(3)
3	45	F	14 days	After COVID-19	Bilateral centrum semiovale and corona radiata	Not specified	(4)
4	40s	F	9 days	After COVID-19	Bilateral frontoparietal white matter	Not specified	(5)
5	60	F	15 days	Before COVID-19	Left corona radiata	p.Arg332Cys	(6)
6	28	M	Asymptomatic	After COVID-19	Bilateral centrum semiovale	Not specified	(7)
7	64	M	3 days	After COVID-19	Bilateral corona radiata	Not specified	(8)
8	30	F	10 days	After COVID-19	Bilateral centrum semiovale	p.Cys440Trp	(9)
9	58	F	7 days	Before COVID-19	Bilateral centrum semiovale, genu of the corpus callosum	p.Tyr150Cys	(10)
10	47	M	9 days	Before COVID-19	Bilateral centrum semiovale, genu of the corpus callosum, bilateral MCPs	p.Arg90Cys	(10)
11	40	M	11 days	Before COVID-19	Bilateral centrum semiovale, bilateral MCPs	p.Cys108Arg	(10)
12	59	M	4 days	After COVID-19	Bilateral centrum semiovale, bilateral MCPs	p.Arg169Cys	The present case

COVID-19: coronavirus disease 2019, CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, DWI: diffusion-weighted imaging, M: male, F: female, MCPs: middle cerebellar peduncles

cases of bilateral MCP lesions in patients with both COVID-19 and CADASIL have recently been reported (10). The MCP is mainly supplied by the anterior inferior cerebellar artery (AICA) but also receives blood supply from the superior cerebellar artery, which is connected to the terminal branches of the AICA. Consequently, the MCP is considered a watershed region between these two arteries (15). While watershed infarction is not common in CADASIL (16), it may occur in patients with both COVID-19 and CADASIL (10). The present case provides additional support for the hypothesis that COVID-19 can increase the risk of watershed infarction.

In conclusion, when evaluating a patient with COVID-19 who presents with bilateral MCP lesions, it is essential to consider the possibility of acute cerebral infarction and check for underlying medical conditions, such as CADASIL.

This study was approved by the Institutional Review Board of the International University of Health and Welfare. The patient provided his written informed consent for this conduct of this study and the publication of its findings.

The authors state that they have no Conflict of Interest (COI).

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