INTERNAL MEDICINE

□ CASE REPORT □

CADASIL Presenting as Acute Bilateral Multiple Subcortical Infarcts without a Characteristic Temporal Pole or Any External Capsule Lesions

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Abstract

A 37-year-old man was hospitalized for an evaluation of acute bilateral multiple subcortical infarcts. There were no specific signal abnormalities in the temporal pole or external capsule. An abdominal skin biopsy showed granular, electron-dense, osmiophilic material (GOM) in the smooth muscle cells on electron microscopy. A direct sequencing analysis of *NOTCH3* revealed a heterozygous c.986G>A substitution in exon 6, resulting in a Cys329Tyr amino acid replacement. According to these findings, the patient was diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencehalopathy (CADASIL). Thus, early phases of CADASIL can present as acute bilateral multiple subcortical infarcts without a characteristic temporal pole or any external capsule lesions.

Key words: CADASIL, *NOTCH3*, GOM, stroke

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Introduction

Mutations of the *NOTCH3* gene on chromosome 19 cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), an inherited small artery disease of mid-adulthood (1). Magnetic resonance imaging (MRI) findings of CADASIL include focal lacunar infarcts and diffuse T2-weighted hyperintensities or leukoaraiosis. Furthermore, T2-weighted hyperintensities in the temporal pole and external capsule are characteristic findings that help to distinguish the disease (2). We herein report an unusual case of CADASIL presenting as acute bilateral multiple subcortical infarcts without demonstrating the characteristic MRI findings.

Case Report

A 37-year-old Japanese man was admitted for dysarthria. Six days prior to admission, he was able to play baseball as usual. Four days prior to admission, he experienced speech and gait difficulties, and his colleague noted a general slowing of his speech and thought processes. The patient had a medical history of gouty arthritis and adolescent-onset migraine without aura. He had no history of hypertension, diabetes mellitus, or dyslipidemia. He smoked half a pack of cigarettes per day for 20 years and drank socially. He took no medications or illicit drugs. He had two siblings, and there was no family history of headache, stroke, or dementia; his father died because of a myocardial infarction at 55 years of age.

On admission, he was oriented to place and person. His Glasgow Coma Scale score was 14/15. A neurological examination revealed paralytic dysarthria and mild left-sided paralysis. He had cognitive impairment, and his Revised Hasegawa Dementia Scale (HDS-R) was 13/30 (age 1/1, orientation in time 4/4, orientation in place 2/2, repeating 3 words 3/3, serial subtractions of 7s 1/2, digits backward 0/2,

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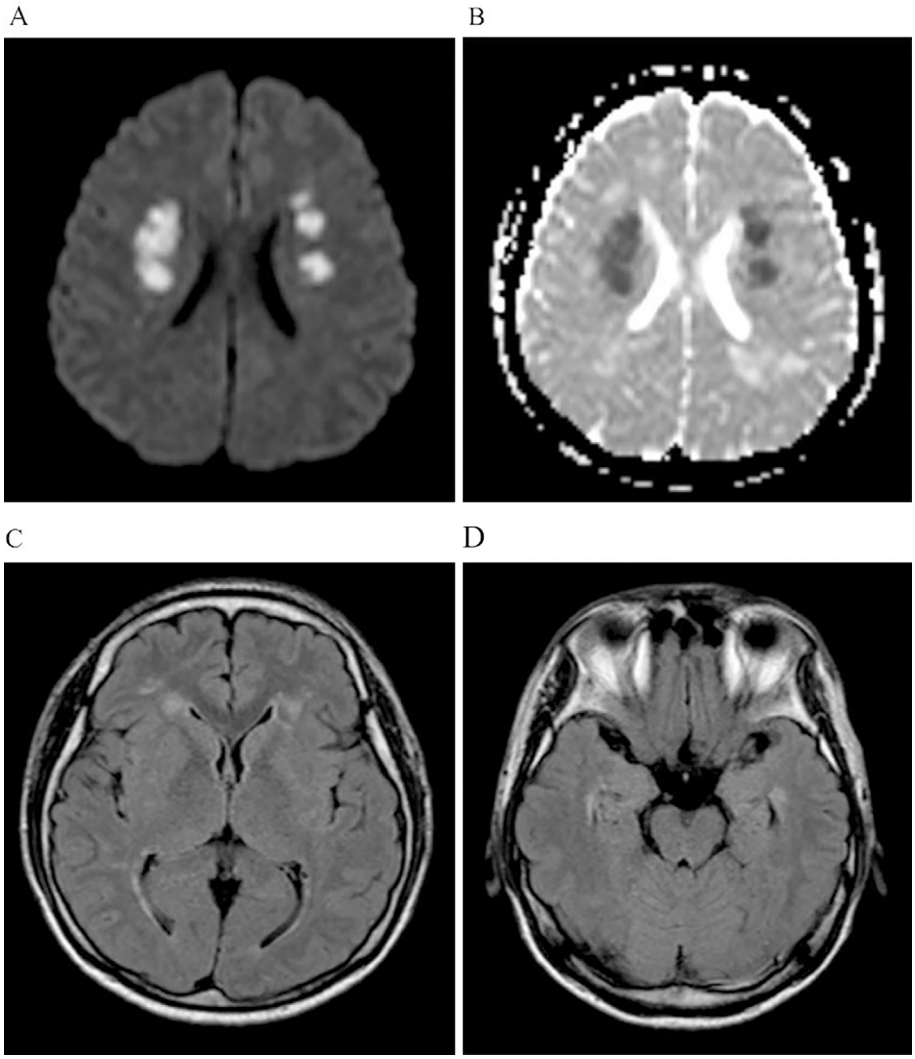

Figure 1. Diffusion weighted imaging (DWI) revealed multiple high intensities in the corona radiata and bilateral periventricular white matter (A). The apparent diffusion coefficient values were low in concurrence with the high intensities on DWI (B). The fluid-attenuated inversion recovery (FLAIR) sequence did not show specific signal abnormalities at the temporal pole or external capsule. There were high intensities in the periventricular region (C, D).

recalling 3 words 0/6, recalling 5 objects 2/5, and generating vegetables 0/5) (3). His modified Rankin Scale score was 2.

Diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) revealed multiple areas of high intensities in the corona radiata and bilateral periventricular white matter (Fig. 1A). The apparent diffusion coefficient values were low in concurrence with the high intensities on DWI (Fig. 1B). There were no specific signal abnormalities in the temporal pole or external capsule on the FLAIR sequence (Fig. 1C and D). T2*-weighted imaging showed no microbleeds or hemorrhages. Magnetic resonance angiography and venography revealed no abnormalities. Transthoracic echocardiography, carotid ultrasonography, and 24-hour Holter monitoring findings were normal. Transesophageal echocardiography was not performed because the patient did not provide his consent. The computed tomography scans of his chest, abdomen, and pelvis were normal. The hypercoagulability work-up proved to be unremarkable. A cerebrospinal fluid analysis showed a normal protein level and no pleocytosis. Oligoclonal bands were also negative in the cerebrospinal fluid.

The patient was treated with oral aspirin, and his condition gradually improved with rehabilitation. The time course of his symptoms and MRI findings were consistent with an ischemic stroke. Because the bilateral multiple ischemic lesions were confined to the deep white matter and did not affect the cerebral cortex, his stroke was thought to be due to small vessel disease. In addition, he had a migraine. Therefore, additional examinations were performed. An abdominal skin biopsy showed granular, electron-dense, osmiophilic material (GOM) in the smooth muscle cells on electron microscopy (Fig. 2). Informed consent was obtained from the patient, and approval for this study was obtained from the University Ethical Committee. Genomic DNA was extracted from the peripheral blood, and a direct sequencing analysis of *NOTCH3* revealed a heterozygous c.986G>A substitution

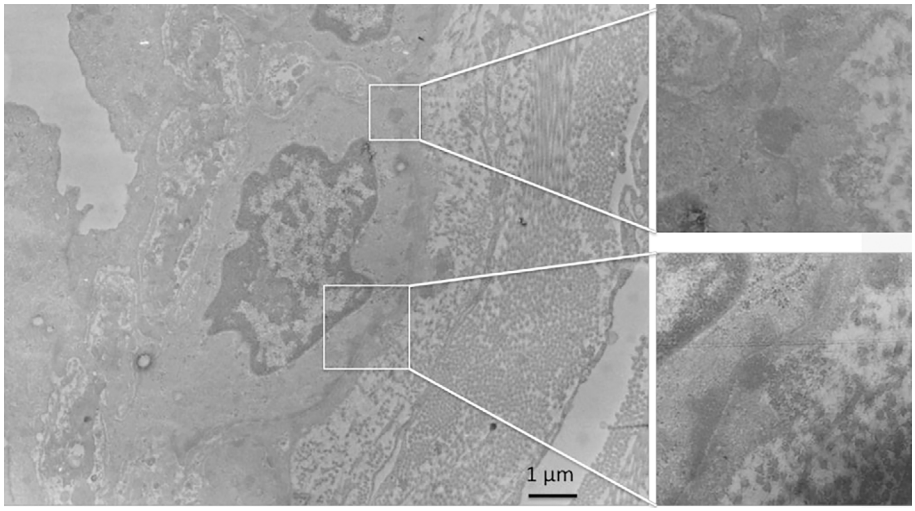

Figure 2. An abdominal skin biopsy showed granular, electron-dense, osmiophilic material (GOM) in the smooth muscle cells on electron microscopy.

in exon 6, resulting in a Cys329Tyr amino acid replacement. The patient fulfilled the diagnostic criteria, except for any family history, and other conditions, such as multiple sclerosis and leukodystrophy, were unlikely (4). Thus he was diagnosed with CADASIL.

The patient was ultimately transferred to a rehabilitation center. At a follow-up visit three months later, his dysarthria, hemiplegia, and vascular dementia had recovered dramatically by rehabilitation. His HDS-R was improved to 27/30, and he was able to work again. Follow-up MRI revealed no new-onset infarcts or hemorrhages. He was treated with cilostazol and lomerizine after discharge and has shown no signs of relapse in clinical and MRI findings for five years.

Discussion

The present case reveals two important suggestions in clinical practice. First, patients with CADASIL may not present with characteristic temporal pole and external capsule lesions. Because of its high sensitivity, the involvement of the anterior temporal lobe and external capsule on MRI aids in the diagnosis of CADASIL. The sensitivity and specificity of diagnosing CADASIL following moderate or severe involvement of the anterior temporal pole on MRI was 89% and 86%, respectively, whereas involvement of the external capsule had a high sensitivity of 93%, but a low specificity of 45% (5). Involvement of the anterior temporal lobe may be occasionally absent, especially in the Asian CADASIL population (6, 7). To the best of our knowledge, cases of CADASIL presenting with symptomatic ischemic stroke without both temporal pole and external capsule lesions is quite rare. Subcortical lacunar lesions are also abnormal MRI findings that occur in CADASIL patients, and this finding has a sensitivity of 59% and specificity of 100% (8). The present patient did not have these characteristic MRI findings and was considered to be in the early phases of the disease. However, he had T2-weighted hyperintensities in the periventricular region, which appeared to be incompatible to his age and risk factors. White matter hyperintensities in the periventricular region are known to be one of the first imaging signs of CADASIL and often appear before its clinical onset (6). White matter hyperintensities increase with age, however, incompatible white matter lesions in the periventricular region of young adults may assist in diagnosing the early phase of CADASIL.

Second, CADASIL can present as acute bilateral multiple subcortical infarcts. Generally, multiple acute ischemic strokes are of cardioembolic or atherothrombotic origin. However, in a previous study, small vessel disease was identified to be a cause of acute multiple subcortical strokes (9). Another study reported that a cardioembolic or atherothrombotic stroke mechanism was rare for acute simultaneous multiple lacunar infarcts (10). A patient that presented with acute simultaneous multiple subcortical infarcts as the first manifestation of CADASIL has also been reported (11). The precise pathophysiology of these infarcts remains unclear. In CADASIL patients, *NOTCH3* extracellular domain accumulates in arterial walls followed by vascular smooth muscle cell degeneration and subsequent fibrosis and stenosis of arterioles, predominantly in the cerebral white matter (12). When unknown factors are added, acute bilateral multiple subcortical infarcts may occur because of diffuse vascular smooth muscle cell degeneration. It is therefore important to include CADASIL in the differential diagnosis when encountering cases demonstrating acute multiple subcortical infarcts.

The actual frequency of CADASIL is unclear. The prevalence of *NOTCH3* gene mutations has been reported to be approximately 4.14/100,000 adults (13). CADASIL has an autosomal dominant inheritance. However, a *de novo* mutation has been reported (14); therefore, the absence of family history does not exclude CADASIL, as in the present patient.

In conclusion, early phases of CADASIL can present with

ischemic strokes without characteristic temporal pole and external capsule lesions. Acute bilateral multiple subcortical infarcts can occur as a manifestation of CADASIL. When temporal lobe and external capsule lesions are absent, white matter lesions in the periventricular region, which are incompatible with patient risk factors, may assist in the diagnosis of the early phase of CADASIL.

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

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