

# Cognitive Impairment and Cerebral Hypoperfusion in a CADASIL Patient Improved During Administration of Lomerizine

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**Abstract:** A 64-year-old woman was admitted to our hospital for recurrent stroke and cognitive impairment and was diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Iodine-123 iodoamphetamine single photon emission computed tomography showed hypoperfusion in the whole brain, but cerebral blood flow increased dramatically after the administration of acetazolamide in the cerebral cortex. Lomerizine, a diphenylmethylpiperazine  $\text{Ca}^{2+}$  channel blocker, can selectively increase cerebral blood flow. Cognitive decline and cerebral hypoperfusion improved during 2-year administration of lomerizine in this CADASIL patient, and thus, lomerizine is a potential candidate for treating cognitive impairment in CADASIL patients.

**Key Words:** CADASIL, lomerizine, IMP SPECT, acetazolamide

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy due to a Notch3 mutation, leading to initial migraine, cerebral infarction, and finally, vascular dementia.<sup>1</sup> There has been no data to demonstrate the efficacy of any medication for CADASIL, although antithrombotic agents such as aspirin are currently being used. Lomerizine, a diphenylmethylpiperazine  $\text{Ca}^{2+}$  channel blocker clinically used as an oral anti-migraine drug,<sup>2</sup> selectively increases cerebral blood flow (CBF) in an animal model.<sup>3</sup> We report here that cognitive decline and cerebral hypoperfusion improved during the 2-year administration of lomerizine in a CADASIL patient.

## CASE REPORT

The patient was a 64-year-old woman who frequently made errors in calculations from January 2005. Her first attack manifested as difficulty in handwriting and swallowing in May 2005, and she visited a nearby hospital. Magnetic resonance imaging (MRI) revealed multiple cerebral infarction, and aspirin was given. In June 2005, she was admitted to our hospital for

renal dysfunction, and renal biopsy revealed deposits of immunoglobulin A on the glomerulus. During admission, dysarthria and dizziness progressed, and she was referred to our department in July 2005. Aspirin 100 mg, dipyridamole 300 mg, losartan 50 mg, lansoprazole 15 mg, and etizolam 0.5 mg were administered once a day from May 2005, and these medications continued throughout the treatment period. Her mother died of a stroke at age of 49 years, and her brother had migraines and died of mental disease at age of 69 years.

On admission, physical examination revealed a blood pressure of 107/64 mm Hg and regular pulse rate of 68 beats per minute. She had a depressive mood and complained of anxiety about her symptoms and daily life. Neurological examination revealed saccadic eye movement, dysarthria, and dysphagia. The finger-nose-finger test and heel-to-knee test revealed dysmetria and decomposition at the right side. Deep tendon reflexes increased bilaterally. She stood up with a wide base, and her gait was ataxic. Her Mini-Mental State Examination (MMSE) score was 16/30. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) revealed that her total IQ was 59, verbal IQ was 66, and performance IQ was 55. The performance subset raw scores in WAIS-R, specifically for block design and digit symbol, were low at 1 and 2, respectively. The Zung index was 66.8%.

Brain MRI revealed a diffuse T2 high-intensity signal at the bilateral deep cerebral white matter extending from the temporal pole and frontal lobe. Diffusion-weighted imaging showed acute infarction at the right cerebellar peduncle and the bilateral cerebral white matter (Fig. 1). Magnetic resonance angiography revealed no abnormalities. Iodine-123 iodoamphetamine single photon emission computed tomography (<sup>123</sup>I-IMP SPECT) revealed diffuse low CBF in the cerebral cortex and a severe decrease in the right cerebellum and the bilateral inferior temporal lobe (Fig. 2A). The mean quantitative regional CBF (rCBF) using <sup>123</sup>I-IMP and a single blood sample<sup>4</sup> was 27.4 mL/100 g per minute in the whole cerebral cortex. Genetic analysis revealed a heterozygous missense C-to-T mutation at nucleotide 499 of Notch3. This mutation yields an Arg141Cys substitution within the epidermal growth factor-like repeat domain of the notch protein. She was diagnosed with CADASIL.

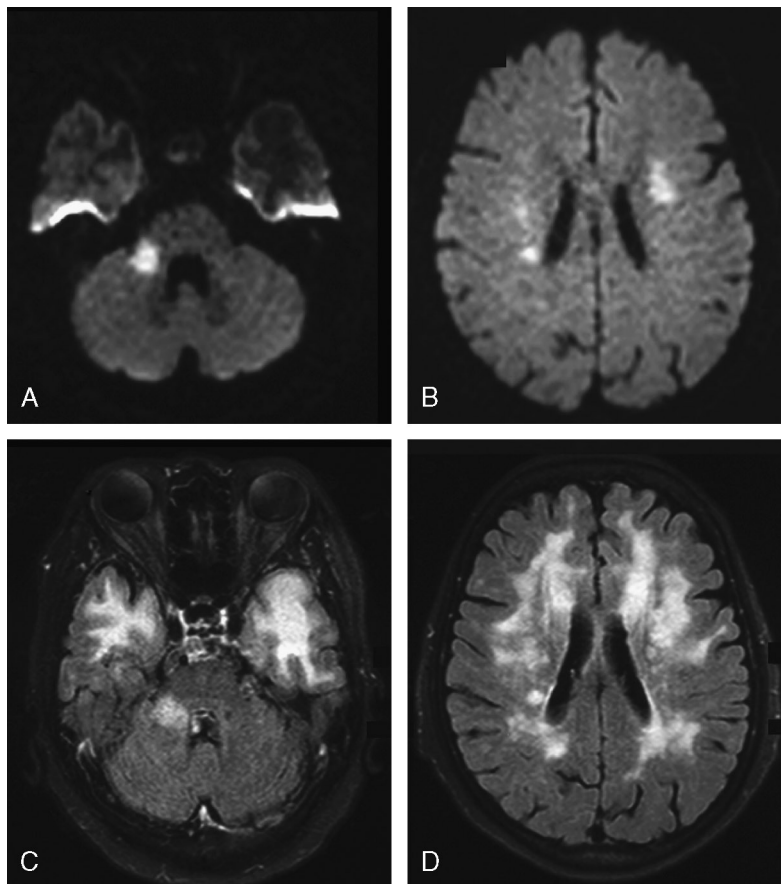
Iodine-123 iodoamphetamine single photon emission computed tomography after acetazolamide showed that the rCBF of each cortex had dramatically increased to more than 70 mL/100 g per minute. This dramatic response of rCBF to acetazolamide gave us the idea of oral administration of acetazolamide. However, acetazolamide can affect immunoglobulin A nephritis, and we thus chose a therapeutic trial of lomerizine based on its selective increase of CBF. Informed consent was obtained from the patient and her husband. After an 8-week trial

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**FIGURE 1.** Diffusion-weighted images on admission revealed acute infarction in the right cerebellar peduncle (A) and bilateral periventricular white matter (B). Fluid attenuation inversion recovery images on admission revealed a high-intensity signal at the bilateral deep cerebral white matter extending from the temporal pole (C) and frontal lobe (D).

of lomerizine, her MMSE score increased to 21, and WAIS-R revealed improvement to a total IQ of 70, verbal IQ of 80, and performance IQ of 62 in October. The block design and digit symbol raw scores improved to 4 and 4, respectively. The other performance subsets and most of the verbal subsets of WAIS-R improved to more than twice the level before treatment. However, her depressive state continued after the start of lomerizine administration. To date, medications for dementia such as donepezil, rivastigmine, and memantine have not been administered to this patient. Quantitative  $^{123}\text{I}$ -IMP SPECT in October 2005 revealed an increase in the cortical CBF (40.4 mL/100 g per minute) (Fig. 2B).

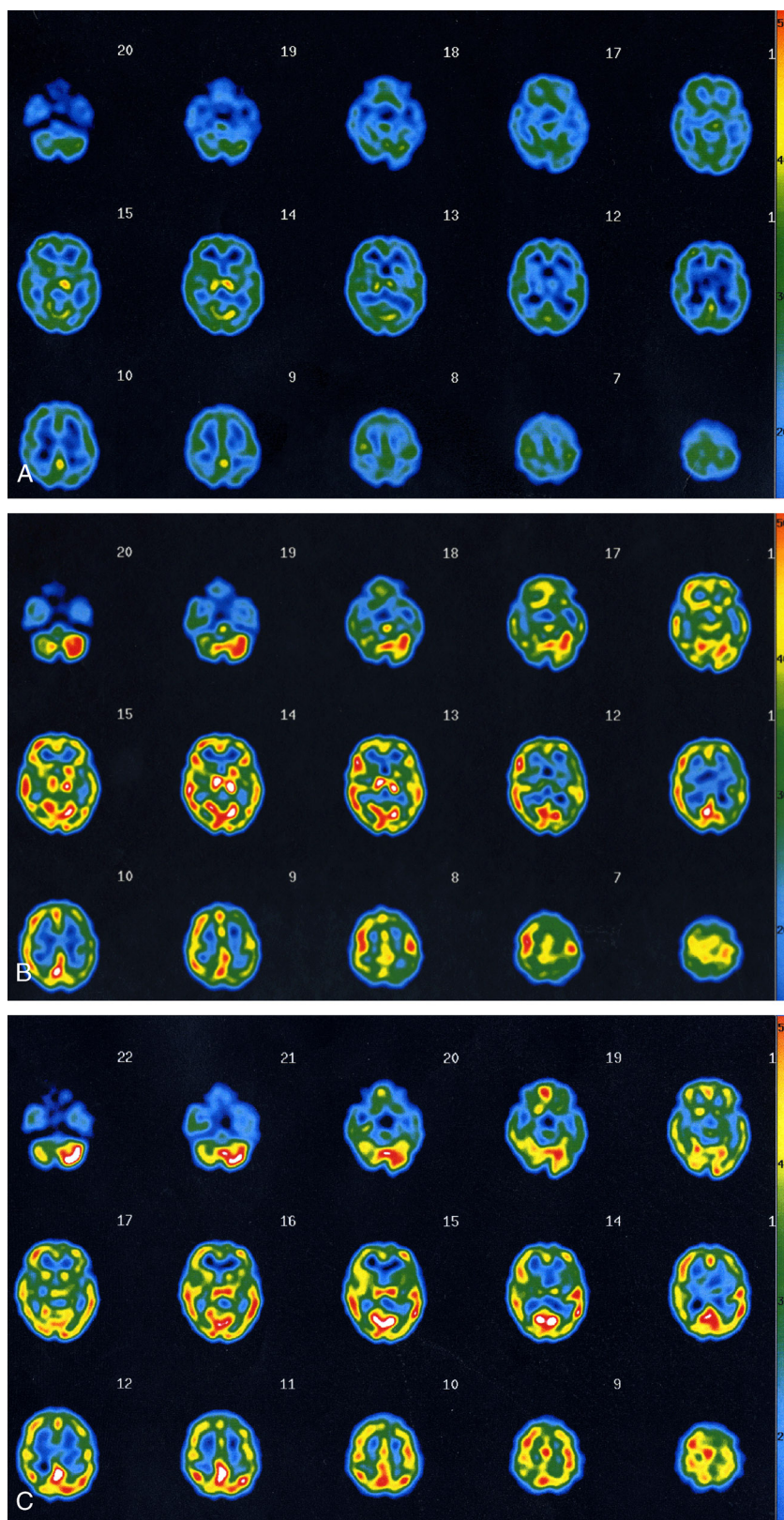
On the basis of these results, we continued to administer lomerizine to the patient for 2 years. Her depressive state continued after the start of lomerizine administration, and thus, 8 weeks later, a psychiatrist prescribed sulpiride and maprotiline. A selective serotonin reuptake inhibitor was also started from January 2006 but was discontinued 5 months later because of adverse effects. Her depressive symptoms, particularly anxiety, could not be resolved with administration of antidepressants. Two years after the start of lomerizine treatment, the patient preserved cognitive function and CBF. Her MMSE was 23, and WAIS-R revealed a total IQ of 76, verbal IQ of 85, and performance IQ of 69. The block design and digit symbol scores in WAIS-R improved to 5 and 6, respectively. The scores of the other performance and verbal subsets of WAIS-R, except

similarities, were maintained after the start of lomerizine administration. Quantitative  $^{123}\text{I}$ -IMP SPECT in June 2007 revealed a mean cortical rCBF of 49.4 mL/100 g per minute, although rCBF in the inferior temporal lobe was still low (25.7 mL/100 g per minute) (Fig. 2C).

## DISCUSSION

Acetazolamide has been reported to be effective for the migraine of CADASIL patients,<sup>5</sup> but it is unclear whether acetazolamide is effective for stroke. A recent study of acetazolamide infusion resulted in a significant increase in CBF in a CADASIL patient even in areas of low CBF before infusion.<sup>6</sup> Our quantitative single photon emission computed tomography data from this CADASIL patient support the vasoreactivity to acetazolamide in CADASIL. At first, we hypothesized that acetazolamide might be useful for CADASIL patients but were alerted by a nephrologist to the possibility that acetazolamide might affect the renal tubular function of this patient. Lomerizine is a  $\text{Ca}^{2+}$  channel blocker that dilates cerebral vessels selectively and is used clinically for migraines.<sup>2,3</sup> Lomerizine also has a protective effect against experimental ischemia and hypoxia in an animal model.<sup>7</sup> Therefore, we hypothesized that lomerizine may be suitable for the treatment of CADASIL.

Neuropsychological tests revealed that the cognitive decline of our patient progressed in July and August 2005 after the second stroke event, although cerebellar signs and motor



**FIGURE 2.** Quantitative  $^{123}\text{I}$ -IMP SPECT before administration of lomerizine (A). Quantitative  $^{123}\text{I}$ -IMP SPECT at 8 weeks after administration of lomerizine (B). Quantitative  $^{123}\text{I}$ -IMP SPECT at 2 years after administration of lomerizine (C).



dysfunction improved. Mean rCBF in the whole cerebral cortex also markedly decreased in August before administration of lomerizine. This cognitive decline corresponds with a previous report in which a CADASIL patient with new stroke events revealed acute cognitive decline with marked and persistent worsening of cognitive performance.<sup>8</sup> To exclude the observed improvements in cognitive function and CBF being due to spontaneous recovery from the acute stroke event in this case, the cognitive disturbance and CBF levels manifest at 2 months after stroke onset was set as the baseline data. We confirmed that this improvement was maintained for 2 years. We believed that the decrease in CBF in the whole cerebral cortex at the baseline was due to chronic progressive multiple cerebral infarcts and not to acute infarcts at the cerebellar hemisphere and corona radiata. Several studies<sup>9–11</sup> have described significant decreases in the CBF at basal ganglia and the white matter with acute lacunar infarction and ischemic leukoaraiosis by positron emission tomography or perfusion MRI study, but the decreases in CBF were limited to the infarcted area and did not extend to the gray matter. In contrast, CBF and cerebral metabolic rate of oxygen<sub>2</sub> in patients with multiple cerebral infarcts and dementia decreases significantly, particularly in the frontal and parietal cortices in chronic stage.<sup>12</sup> In the present patient, frontal symptoms such as initial hesitation of gait, executive dysfunction, and apathy deteriorated during July and August 2005 and ameliorated after lomerizine was administered. Based on the clinical course and imaging analysis, the improvement in frontal dysfunction seen in this patient can be speculated to have been due to lomerizine improving CBF and not to the natural course from small strokes.

Lomerizine has previously been reported to increase the CBF by more than 10% compared with baseline in an animal model.<sup>3</sup> Harada et al<sup>13</sup> analyzed the effects of lomerizine on rCBF using focal cerebral ischemia model in a cat and found significant protective effects against the reduction in CBF. Furthermore, lomerizine has been reported to inhibit both T- and L-type Ca<sup>2+</sup> currents<sup>14</sup> to be effective at preventing glutamine-induced neurotoxicity<sup>15</sup> and to improve the reduced respiratory activity of mitochondria and the reductions in pyruvate and adenosine triphosphate in brain energy metabolism after brain ischemia.<sup>7</sup> Nimodipine and flunarizine, dihydropyridine calcium antagonists, may improve symptoms of cognitive dysfunction in elderly patients by dilating cerebral blood vessels and increasing CBF experimentally and clinically.<sup>16</sup> Lomerizine has been reported to dilate vessel and protect neuronal cell more than nimodipine and flunarizine.<sup>3</sup> These effects of lomerizine may explain the increase in the CBF and viability of neuronal cell and plasticity of synapses.

Although we did observe recovery of cognitive impairment and CBF during lomerizine administration for 2 years, only a single case was involved, and thus, a pilot study is required to determine whether this effectiveness of lomerizine on CADASIL occurs in other CADASIL patients. In addition, long-term follow-up is also required to determine whether lomerizine is effective in preventing stroke in CADASIL. The improvement in cognitive impairment and the increase in CBF observed in this case, without adverse effects, suggest that lomerizine should undergo a more rigorous testing for efficacy in CADASIL patients.

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## REFERENCES

- Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;383:707–710.
- Hara H, Shimazawa M, Hashimoto M, et al. Anti-migraine effects of lomerizine. *Nippon Yakurigaku Zasshi* 1998;112(suppl 1): 138P–142P.
- Hara H, Shimazawa M, Sasaoka M, et al. Selective effects of lomerizine, a novel diphenylmethylpiperazine Ca<sup>2+</sup> channel blocker, on cerebral blood flow in rats and dogs. *Clin Exp Pharmacol Physiol* 1999;26:870–876.
- Iida H, Itoh H, Nakazawa M, et al. Quantitative mapping of regional cerebral blood flow using iodine-123-IMP and SPECT. *J Nucl Med* 1994;35:2019–2030.
- Forteza AM, Brozman B, Rabinstein AA, et al. Acetazolamide for the treatment of migraine with aura in CADASIL. *Neurology* 2001;57:2144–2145.
- Chabriat H, Pappata S, Ostergaard L, et al. Cerebral hemodynamics in CADASIL before and after acetazolamide challenge assessed with MRI bolus tracking. *Stroke* 2000;31:1904–1912.
- Yamashita A, Ozaki A, Ikegami A, et al. Effects of a new diphenylpiperazine calcium antagonist, KB-2796, on cerebral ischemic neuronal damage in rats. *Gen Pharmacol* 1993;24:1473–1480.
- Peters N, Herzog J, Opherk C, et al. A two-year clinical follow-up study in 80 CADASIL subjects: progression patterns and implications for clinical trials. *Stroke* 2004;35:1603–1608.
- Markus HS, Lythgoe DJ, Ostergaard L, et al. Reduced cerebral blood flow in white matter in ischaemic leukoaraiosis demonstrated using quantitative exogenous contrast based perfusion MRI. *J Neurol Neurosurg Psychiatry* 2000;69:48–53.
- O'Sullivan M, Lythgoe DJ, Pereira AC, et al. Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. *Neurology* 2002;59:321–326.
- Yamaguchi S, Fukuyama H, Yamauchi H, et al. Hemodynamics in the cerebral cortex and basal ganglia—observation on normal volunteers and patients with lacunes using PET. *Rinsho Shinkeigaku* 1991;31:1070–1076.
- Kitamura S, Terashi A, Araki T, et al. Cerebral hemodynamics in multiple cerebral infarction with or without dementia. *Nippon Ronen Igakkai Zasshi* 1989;26:557–562.
- Harada K, Nakasu Y, Matsuda M, et al. Effects of a new Ca<sup>2+</sup> antagonist, KB-2796, on the regional cerebral blood flow and somatosensory evoked potentials in the ischemic brain in cats. *Surg Neurol* 1988;30:89–96.
- Akaike N, Ishibashi H, Hara H, et al. Effect of KB-2796, a new diphenylpiperazine Ca<sup>2+</sup> antagonist, on voltage-dependent Ca<sup>2+</sup> currents and oxidative metabolism in dissociated mammalian CNS neurons. *Brain Res* 1993;619:263–270.
- Hara H, Yokota K, Shimazawa M, et al. Effect of KB-2796, a new diphenylpiperazine Ca<sup>2+</sup> antagonist, on glutamate-induced neurotoxicity in rat hippocampal primary cell cultures. *Jpn J Pharmacol* 1993;61:361–365.
- Wadworth AN, McTavish D. Nimodipine. A review of its pharmacological properties, and therapeutic efficacy in cerebral disorders. *Drugs Aging* 1992;2:262–286.