—Case Reports—

Recovery of Normal Hemodynamic Activities after Long-term Medication in a Patient with Left Internal Carotid Arterial Occlusion

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Abstract

Background and Objective: Aspirin, clopidogrel, cilostazol, and statins are thought to reduce the risk of cerebral infarction in patients with intracranial arterial stenosis. We present a case of multiple intracranial arterial stenoses in which increased cerebral blood flow (CBF) was demonstrated after long-term medical therapy.

Case Presentation: A 68-year-old man with a history of cerebral infarction showed complete occlusion of the left internal carotid artery with severe stenoses in the A1 segment of the left anterior cerebral artery (ACA) and the left posterior communicating artery resulting in poor visualization of the left middle cerebral artery (MCA) on magnetic resonance angiography (MRA). Administration of aspirin and clopidogrel prevented ischemia from recurring for 1 year; however, the stenoses never improved. Technetium-99m-L, L-ethylcysteinate dimer single-photon emission computed tomography (SPECT) demonstrated a significant decrease in CBF in the territory of the left MCA. Anastomosis between the superficial temporal artery and the MCA was recommended to the patient because no supplementary blood supply was expected through either the left A1 or posterior communicating artery. However, the patient refused surgery because of the associated risks. To enhance vasodilation, clopidogrel was replaced by cilostazol. One year later, the stenoses had partially improved. Further treatment with aspirin, cilostazol, simvastatin, and nateglinide contributed to the significant increase in CBF with normal hemodynamics, as shown with acetazolamide-loading SPECT.

Conclusion: The goal of treatment for intracranial arterial stenosis is to supply sufficient blood flow to the brain rather than to completely dilate the stenotic artery. Long-term treatment with aspirin, cilostazol, simvastatin, and nateglinide might help increase CBF in some patients with intracranial arterial stenosis.

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Key words: aspirin, cerebral blood flow, cilostazol; single-photon emission computed tomography, stenosis

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Introduction

In addition to having an antiplatelet effect, cilostazol has vasodilating effects, protective effects on arterial endothelial cells, and inhibitory effects on smooth-muscle cell proliferation[1–4]. Improvement of some severe intracranial arterial stenoses after treatment with cilostazol has been reported[4,5]; however, some of these stenoses might have been caused by arterial dissection or a cardiac embolus, especially in cases showing rapid improvement. In such cases the improvement of the stenosis might have been unrelated to treatment: Akins et al. have reported that about 20% of intracranial arterial stenoses improve spontaneously[6]. Many reports describe only dilation of arterial stenosis on magnetic resonance angiography (MRA) after treatment with cilostazol but do not describe cerebral blood flow (CBF)[5,7]. We present a case of intracranial arterial stenoses in which CBF markedly increased after long-term treatment with cilostazol.

Case Report

In March 2006 a 68-year-old man with hyperlipidemia and diabetes mellitus had a history of cerebral infarction but recovered without neurological deficits. Since then, he had been taking aspirin (100 mg once a day), simvastatin (10 mg once a day), and nateglinide (90 mg 3 times a day). The patient was referred to our clinic for follow-up MRA and magnetic resonance imaging (MRI) in September 2007. The fasting blood glucose level was 112 mg/dL, hemoglobin A_{1c} (HbA_{1c}) was 6.4%, total cholesterol was 207 mg/dL, and low-density lipoprotein (LDL) cholesterol was 111 mg/dL. In October 2007 MRI showed an old cerebral infarction in the left corona radiata (**Fig. 1A**), and MRA revealed complete occlusion of the left internal carotid artery (ICA), severe narrowing of the A1 segment of the left anterior cerebral artery (ACA) and the left posterior communicating (P-com) artery causing poor visualization of the left middle cerebral artery (MCA) (**Fig. 1B**). Clopidogrel (75 mg once a day) was additionally prescribed, but hemorrhage occurred in the right ocular fundus in September

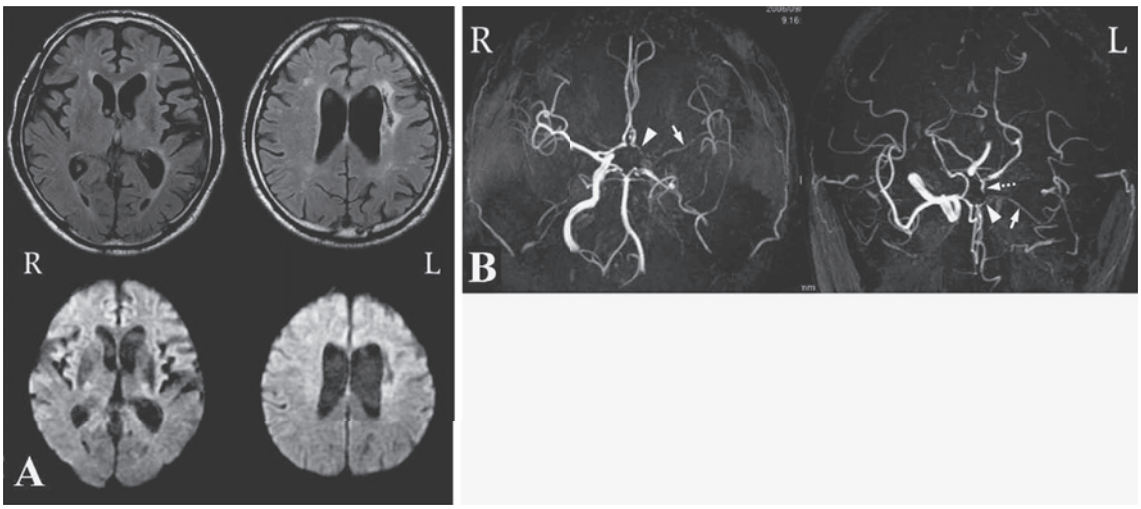

Fig. 1 MRI and MRA in 2007

A: MRI: Old cerebral infarction is identified in the left corona radiata as a low-intensity area on both fluid-attenuated inversion recovery (upper) and diffusion (lower) imaging.

B: MRA: Complete occlusion of the left internal carotid artery (ICA) is recognized, and severe stenoses are present in the left A1 portion of the anterior cerebral artery (ACA) (**arrowheads**) and in the left posterior communicating (P-com) artery (**arrow with dotted line**) resulting in poor visualization of the left middle cerebral artery (MCA) (**arrows**).

R: right, L: left

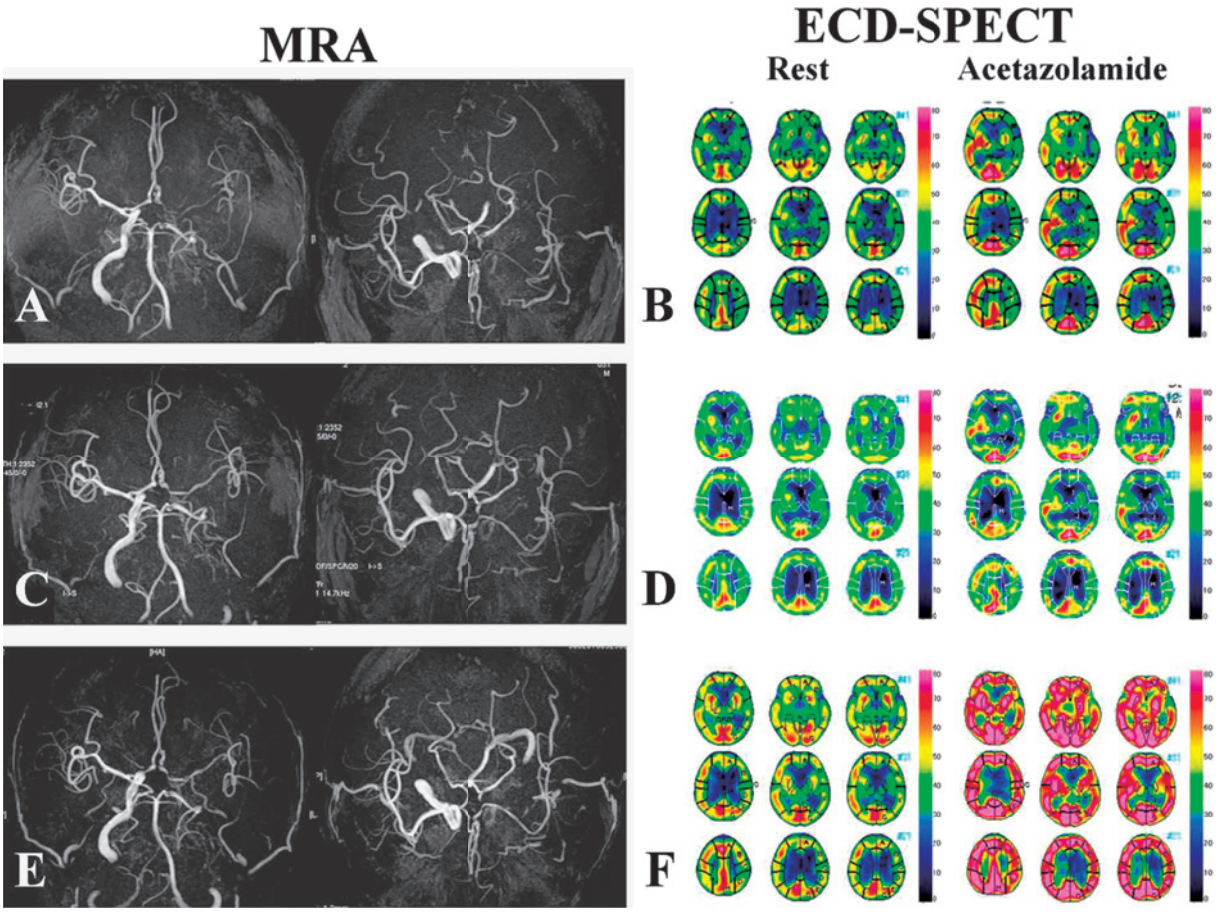

Fig. 2 Follow-up MRA and SPECT

A: MRA in 2008: The left MCA is still poorly visualized because of severe stenoses in the left A1 portion of the ACA and P-com artery.

B: SPECT in 2008: Cerebral blood flow (CBF) at rest in the territory of the MCA is definitely lower on the left than on the right. In particular, the left temporal lobe, angular gyrus, and basal ganglia show poor blood flow. The acetazolamide loading study demonstrates an increase in the right-left difference in CBF.

C: MRA in 2009: Definite enlargement of the left MCA because of partial dilation of both the left A1 segment of the ACA and P-com artery is identified.

D: SPECT in 2009: No increase in CBF was identified in either the resting state or the acetazolamide loading state.

E: MRA in 2010: No further dilation of the left MCA is seen compared with MRA in 2009.

F: SPECT in 2010: CBF in the resting condition is slightly increased compared with that seen on SPECT in 2008 or 2009, and, furthermore, the CBF after acetazolamide injection increases significantly to the standard level in both hemispheres with little right-left difference.

2008. Treatment with aspirin was restarted after treatment with aspirin and clopidogrel had been discontinued for 1 month. Follow-up MRA and technetium-99m-L, L-ethylcysteinate dimer single-photon emission computed tomography (SPECT) were performed in October 2008. No improvement of the arterial stenoses was identified **(Fig. 2A)**. Under resting conditions the CBF in the territory of the MCA was slightly lower on the left than on the right, and the right-left difference in CBF increased after acetazolamide injection because of the poor response of the left MCA **(Fig. 2B)**.

We offered anastomosis of the superficial temporal artery to the MCA, because no supplementary blood supply was expected through either the left A1 or left P-com artery. However, the patient refused surgery because of the associated risks. Therefore, cilostazol (50 mg twice a day) was added to aspirin, simvastatin, and nateglinide. One year later, MRA demonstrated dilation of the left A1 and the left MCA **(Fig. 2C)**. In contrast, SPECT showed no improvement in CBF and a poor response to

acetazolamide **(Fig. 2D)**. The medications were continued with an expectation of further dilation of the stenotic arteries. After 2 years of treatment with aspirin, cilostazol, simvastatin, and nateglinide, follow-up MRA in 2010 showed little dilation of the arteries **(Fig. 2E)**. However, SPECT demonstrated considerable improvement in the CBF; the CBF in both hemispheres had increased with little right-left difference under resting conditions and increased markedly after acetazolamide injection **(Fig. 2F)**. The patient has been visiting our clinic regularly without any ischemic attacks, and all medications have been continued.

Discussion

The successful treatment of intracranial arterial stenosis in patients with a history of ischemic attacks may require administering multiple antiplatelet agents[8,9], but enhancing only antiplatelet activity is not always advantageous because of the increased risk of hemorrhage[10]. Unfortunately, in our patient antiplatelet medications had to be temporarily discontinued because of hemorrhage in the right optic fundus caused by the combination of aspirin and clopidogrel, but the treatment never improved either the intracranial arterial stenosis or the hypoperfusion in the territory of the left MCA **(Fig. 2A and 2B)**.

Hemorrhage did not occur after clopidogrel was replaced by cilostazol. We concluded that the combination of aspirin and clopidogrel was more likely to cause bleeding than was the combination of aspirin and cilostazol[11,12]. It is not certain whether the combination of aspirin, simvastatin, nateglinide, and cilostazol is more effective for treating intracranial arterial stenosis than is cilostazol alone, because statins also improve cerebral vasomotor reactivity[13], but cilostazol was definitely associated with the improvement of arterial stenoses in the present case. Additional actions of cilostazol, including vasodilation, protection of arterial endothelial cells, and inhibition of vascular smooth-muscle proliferation[1-4], certainly contributed to the regression of arterial stenosis and might be associated with the improvement in hemodynamic activity in the ischemic lesion. These actions of cilostazol could have affected the right cerebral hemisphere, where no arterial stenosis was identified, resulting in the increase in CBF and the better response to acetazolamide.

The Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis found that progression of intracranial arterial stenosis was significantly less frequent in patients treated with cilostazol for 6 months than in patients who received placebo and that intracranial arterial stenosis regressed in 24.4% of patients receiving cilostazol and 15.4% of patients receiving placebo[5]. The arterial stenoses in our case did not dilate completely and were still recognized on MRA in 2010 **(Fig. 2E)**, but we believe that our treatment for the patient was successful, as shown by SPECT **(Fig. 2F)**. At least 1 study has found that superficial temporal artery-MCA anastomosis provided no benefit over antiplatelet treatment in reducing the risk of ischemic stroke in patients with MCA stenosis[14], but other studies have emphasized the effectiveness of the surgical treatment for patients with intracranial arterial stenosis[15,16]. Neurosurgeons should not be aggressive in surgically treating patients with poorly dilated intracranial arterial stenosis. And long-term follow-up with MRA and SPECT after treatment with multiple antiplatelet agents is important for making appropriate decisions about surgical treatment. The goal of treatment for intracranial arterial stenosis is to supply sufficient blood flow to hypoperfused areas to prevent new ischemic ictus rather than to completely dilate the stenotic artery.

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