Enhancement of the Ivy Sign during an Ischemic Event in Moyamoya Disease

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Abstract:
We herein report a case of increased and expanded ipsilateral ivy sign paralleling the expansion of cerebral infarction in a patient with moyamoya disease. A 67-year-old woman visited our hospital with symptoms of left hemiplegia, left homonymous hemianopia, and left unilateral spatial neglect. Magnetic resonance imaging of the head showed cerebral infarction in the right parietal lobe. In addition, ivy signs were evident on fluid-attenuated inversion recovery imaging. These findings were enhanced by the expansion of cerebral infarction and disappeared once the ischemia resolved, implying hemodynamic changes. As a result of continuing medical treatment without antithrombotic therapy, the patient obtained a good outcome. Treatment for moyamoya disease in the acute phase is considered to require complex knowledge of multiple factors, such as the anatomical background of the individual patient and the progression grade of ischemia.

Key words: moyamoya disease, ivy sign, ischemic event

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Introduction
Moyamoya disease is a progressive cerebrovascular disease that causes stenosis at the ends of the bilateral internal carotid arteries and formation of an abnormal vascular network (moyamoya blood vessels) at the bottom of the brain as collateral circulation (1-3). Occlusion of the main artery may cause ischemic events, while cerebral and intraventricular hemorrhaging may occur due to the development or disruption of the fragile collateral circulation. Characteristic linear hyperintensities along the sulcus on fluid-attenuated inversion recovery (FLAIR) imaging are called the leptomeningeal ivy sign and are considered to represent a slow retrograde flow in the engorged pial vasculature via leptomeningeal anastomosis (4).

We herein report a case of ipsilateral ivy sign that enhanced and expanded with expansion of the cerebral infarction in a patient with moyamoya disease.

Case Report
A 67-year-old woman presented to our hospital with the sudden onset of left hemiparesis (manual muscle testing: 4/5), left homonymous hemianopia, and left unilateral spatial neglect. She had a medical history of hypertension and type 2 diabetes mellitus. The patient was being treated by her family physician with amlodipine (5 mg/day) and metformin (1,000 mg/day), and home blood pressure was in the 120/80 mmHg range. Vital signs on admission were as follows: blood pressure, 155/82 mmHg; heart rate, 78 beats/min; temperature, 36.3°C; respiratory rate, 16 breaths/min; and Glasgow Coma Scale score, 14 (E4V5M5). Laboratory findings showed hyperglycemia (fasting blood glucose level, 165 mg/dL; hemoglobin A1c, 7.8%). Other laboratory findings were unremarkable, including coagulation activity and autoimmune system disease. She had no retinopathy or nephropathy. Echocardiography showed no regional left ventricular motion abnormalities.

Emergent magnetic resonance imaging (MRI) demon-
Figure 1. A) DWI of the head shows cerebral infarction from the right parietal lobe to the right occipital lobe. B) On FLAIR imaging, linear hyperintensities of the sulci are evident in the right cerebral hemisphere. C) MRA shows occlusion of the terminal portions of the bilateral internal carotid arteries (white arrows) and right PCA (white arrowhead). D) Angiography of the right internal carotid artery shows steno-occlusive changes at the terminal portion of the internal carotid artery and moyamoya blood vessels at the base of the brain. Micro-aneurysm is observed at the periphery of the lenticulostriate artery (black arrow). E) Angiography of the right vertebral artery shows occlusion of the PCA (black arrowhead).

Stratified signal hyperintensity involving the right parietal lobe on diffusion-weighted imaging (DWI) (Fig. 1A). Magnetic resonance angiography (MRA) revealed occlusion of the terminal portions of the bilateral internal carotid arteries and the right posterior cerebral artery (Fig. 1C). FLAIR imaging showed multiple hyperintensities in the subarachnoid space (Fig. 1B). After admission, edaravone was administered by drip infusion, but we did not start antithrombotic drugs, considering the possibility of subarachnoid hemorrhaging. In addition, considering the possibility of hemodynamic ischemic stroke, amlodipine was discontinued, and the blood pressure was controlled to around 160/80 mmHg with continuous intravenous infusion of dopamine hydrochloride at 5-7 μg/kg/min.

However, the neurological deficits were exacerbated, and follow-up MRI one day after admission showed expansion of the infarction territory and prominent signal enhancement of hyperintensities in the subarachnoid space (Fig. 2). We therefore started concentrated glycerin and fructose (200 mL) 3 times a day to prevent the spread of cerebral edema. Five days after admission, angiography showed steno-occlusive changes at the terminal portions of the internal carotid arteries and an abnormal vascular network at the base of the brain, in addition to posterior cerebral artery (PCA) occlusion (Fig. 1D, E). Based on these findings, we diagnosed the patient with moyamoya disease.

Contrast-enhanced MRI revealed enhancement in the subarachnoid space corresponding to the area of hyperintensity on FLAIR imaging (Fig. 3A, B), explaining the ivy sign. Brain single photon emission computed tomography (SPECT) with 123I-N-isopropyl-p-iodoamphetamine showed decreased regional cerebral perfusion in the right parietal lobe on admission and an increase in the hypo-perfused area around the ischemic lesion five days after admission (Fig. 4A, B). Since a micro-aneurysm was observed on angiography (Fig. 1D), we decided not to perform antithrombotic therapy for secondary prevention, considering the risk of aneurysm rupture. No abnormalities were detected on electrocardiography or Holter electrography. The cause of cerebral infarction in the PCA territory was considered to be progression of moyamoya disease.

Following the exacerbation of neurological symptoms, the
Figure 2. The comparison of FLAIR and DWI on admission and at 3, 5, and 23 days after admission. These comparisons show increased and expanded ipsilateral ivy sign paralleling expansion of the cerebral infarction. Five days after admission, progression of cerebral infarction had stopped on DWI, and the ivy sign was also diminished 23 days after admission. All immediate MRI studies were performed on a 1.5-T scanner (Siemens Healthcare, Erlangen, Germany) to examine patients with suspected stroke, including DWI, FLAIR, and MRA. DWI was performed with a standard protocol using the following parameters: field of view (FOV), 220 mm; spatial resolution, 1.7×1.7×5.5 mm; and b-values of 0 and 1,000 s/mm². FLAIR was performed in the axial plane (FOV, 220 mm) with a common spatial resolution of 0.9×0.9×5.5 mm.

Figure 3. Gd-enhanced T1-weighted MRI (A, B) five days after admission reveals enhancement in the subarachnoid space corresponding to hyperintensity on FLAIR imaging.

blood pressure was controlled to around 180/90 mmHg with the continuous intravenous infusion of dopamine hydrochloride at 7-10 μg/kg/min. Five days after admission, the progression of the neurological exacerbation stopped, and the progression of cerebral infarction appeared to have stopped as well based on DWI. Concentrated glycerin and fructose were administered for 14 days, and the dose of dopamine hydrochloride was gradually reduced and discontinued by 14 days after admission. The blood pressure was subsequently controlled to around 150/80 mmHg, and no new neurological symptoms appeared. The ivy sign also diminished 23 days after admission (Fig. 2). Finally, the left homonymous hemianopia and left unilateral spatial neglect gradually improved, but the left hemiparesis remained moderate (manual muscle testing: 4/5).

The patient was transferred to a rehabilitation hospital with a modified Rankin Scale score of 3 at 24 days after admission.
Discussion

We described an interesting case of increased and expanded ipsilateral ivy sign paralleling the expansion of cerebral infarction in a patient with moyamoya disease. The ivy sign is reportedly found in 31-66% of cases of moyamoya disease and often appears in symptomatic cases (5). In terms of clinical significance, one report suggests that this sign reflects a state of decreased cerebral circulatory reserve (6). However, the ivy sign is also reportedly unrelated to the oxygen intake rate or collateral circulation (7). Other studies have speculated that only dilated leptomeningeal vessels, which act to supply blood during ischemia, are visualized (4, 7).

The relationship between the presence of an ivy sign and the expansion of cerebral infarction in the acute phase of cerebral infarction has not been clarified. Interestingly, the presence of the ivy sign has been reported to be a predictor of recurrent cerebral infarction in adults with moyamoya disease (8). This suggests that chronic hypoperfusion may be prone to progress to hemodynamic ischemic stroke. In addition, staging in moyamoya disease is associated with the appearance of ischemic disease. The appearance of infarction in the PCA territory reportedly reflects an increased risk of ischemic stroke as the stage progresses (9). Based on these findings, this case was considered to have involved ischemic stroke because of the presence of the PCA lesion and resulting disease progression. However, the ivy sign showed chronic hypoperfusion, which failed to suppress the progression of hemodynamic cerebral infarction.

In this case, the ivy sign was enhanced by the expansion of cerebral infarction, and it disappeared once ischemia resolved. In particular, three days after admission, the cerebral infarction on DWI appeared to have expanded, paralleling the expansion of the ivy sign, and five days after admission, SPECT findings showed an increased area of hypo-perfusion around the ischemic lesion in the right parietal temporal lobe compared to SPECT on admission. The reason for the enhancement of the ivy sign was presumed to involve reactive dilation of pial blood vessels due to increased flow demands resulting from expansion of the cerebral infarction (10). Furthermore, after the progression of cerebral infarction stopped, the ivy sign was considered to have diminished due to decreased flow demands in the ischemic territory. The patient had an expanded cerebral infarction due to an insufficient blood flow supply from the pial arteries. We considered that the ivy sign had weakened as a result of an increased blood flow from the pial arteries as a result of maintaining the blood pressure at a high level by means of the continuous intravenous infusion of dopamine hydrochloride.

No consensus has been reached regarding the medical treatment for moyamoya disease. In general, pediatric cases often develop with cerebral ischemic symptoms, whereas adult cases often develop with intracranial hemorrhaging in addition to cerebral ischemic symptoms. In the acute phase of ischemia and bleeding, medical treatment, such as blood pressure control and management for increased intracranial pressure, is performed. Although evidence is lacking, the use of edaravone, ozagrel sodium, argatroban, and aspirin is recommended for the treatment of acute ischemic moyamoya disease based on the treatment for acute-onset atherosclerotic cerebral infarction (3).

In the present case, the ischemic lesion expanded despite sufficient blood pressure control and intracranial pressure control with concentrated glycerin and fructose. The accumulation of ischemic cores may have been avoidable with the addition of antithrombotic therapy. However, in this case, due to concerns about subarachnoid hemorrhaging and the presence of micro aneurysm, we were hesitant to use antithrombotic therapy in combination. As a result of continu-
ing medical treatment without antithrombotic therapy, the spread of ischemia was minimized, and poor outcomes were avoided. If antithrombotic therapy had been used in combination, cerebral hemorrhaging might have developed, and the outcome might have been poor. Furthermore, if enhancement of the ivy sign is associated with progression of ischemia, small-molecular-weight dextran may have been useful for preventing progression of ischemia, in terms of increasing circulating plasma volume.

Based on the anatomical considerations, such as the localization of aneurysms at the periphery of the lenticulostriate artery making clipping difficult to perform directly and coil embolization being difficult because of the small vessel diameter, no surgery was performed. Treatment for moyamoya disease is thus considered to require complex knowledge of multiple factors, such as the anatomical background of each patient and the progression grade of ischemia.

**Conclusion**

The ivy sign in moyamoya disease with ischemic onset might enhance and diminish in response to hemodynamic changes, indicating flow demands in the ischemic territory. In particular, enhancement of the ivy sign may be associated with expansion of the ischemic area and warrants personalized medical treatment according to the patient background.

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

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