Factor V Leiden Mutation in Reocclusion After Intra-Arterial Thrombolysis

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Background and Purpose—Reocclusion of intracranial arteries after successful recanalization is associated with poor clinical outcome. The role of Factor V Leiden mutation in intracranial arterial thrombosis/rethrombosis is unclear.

Summary of Report—We report the case of a patient who developed recurrent reocclusions of the middle cerebral artery after intra-arterial thrombolysis for acute ischemic stroke. The patient subsequently underwent transcatheter clot retrieval followed by successful stent-supported angioplasty of the occluded segment. He underwent a detailed workup for thrombophilia. The patient was detected to be heterozygous for Factor V Leiden mutation without any other cause for thrombophilia.

Conclusions—Factor V Leiden mutation could be a contributing etiology for reocclusion after endovascular interventions in stroke. Systematic studies looking for thrombophilic mutations in patients with arterial reocclusion might be warranted. (Stroke. 2009;40:660-662.)

Key Words: acute stroke ■ Factor V Leiden ■ reocclusions ■ rtPA ■ thrombolysis

Distal embolization and arterial reocclusions are observed in nearly one fifth of patients undergoing endovascular thrombolysis for acute ischemic stroke. The exact etiology why this happens in some patients is not known. We investigated the possibility of an inherited thrombophilic state as a cause for multiple reocclusions of the middle cerebral artery (MCA) after initial complete recanalization with intra-arterial recombinant tissue plasminogen activator (rtPA).

Case Report

The patient is a 52-year-old healthy white man who presented with aphasia and right hemiplegia with onset 15 minutes before presentation to a peripheral hospital. In the setting of a high National Institutes of Health Stroke Scale (NIHSS) score of 17, he was started on intravenous rtPA and was transferred to our stroke center for possible “rescue” intra-arterial thrombolysis. The patient was showing signs of clinical improvement at the end of 2 hours, when he arrived at our center. Digital subtraction angiography (DSA) showed complete occlusion of the left MCA M1 segment (Figure 1A). Intra-arterial rtPA infusion resulted in complete recanalization of the left MCA (Figure 1B). The patient regained near-normal neurological status and postprocedure CT scan showed no hemorrhage.

Nearly 20 hours postictus, the patient suddenly developed aphasia with right hemiparesis. Repeat CT head showed a dense MCA sign without any hemorrhage. Repeat DSA showed recurrence of left MCA thrombosis (Figure 2A), and abciximab (ReoPro, total dose 18 mg) was infused intra-arterially resulting in partial recanalization (Figure 2B). The patient regained near-normal neurological status and was started on intravenous abciximab along with oral loading with 325 mg aspirin and 75 mg clopidogrel in addition to high-dose statins (80 mg simvastatin). Echocardiography showed normal ejection fraction without any intracardiac clot or wall motion abnormality. The patient’s neurological status stabilized over the next few days, and he was discharged home after 1 week.

As soon as he reached home, the patient had recurrence of the left MCA symptoms. Repeat CT head showed only hypodensity in the left basal ganglia and left posterior parietal region consistent with recent left MCA infarction. The patient underwent a transcatheter clot retrieval (Mechanical Embolus Removal in Cerebral Ischemia [MERCI] Retrieval System; Concentric Medical Incorporated, South San Francisco, Calif) with partial recanalization of the left MCA (Figure 3A–B). Residual stenosis of the left MCA was treated with stent-supported angioplasty (Figure 3C). The patient regained his neurological functions postprocedure, and he was discharged home 2 days later with only a mild right facial paresis and arm drift. Patient stayed on double antiplatelet agents and high-dose statins. On follow-up after 4 months, he did not have any recurrence of symptoms. Tests for all prothrombotic states were negative except for heterozygosity for Factor V
Leiden mutation. Patient also has a history of early-onset vascular disease mortality in 3 maternal uncles.

Discussion
Clinical deterioration after initial improvement is well documented in patients receiving intravenous rtPA for ischemic stroke and has been attributed to reocclusion. Early reocclusion has also been observed in up to 17% of patients during intra-arterial thrombolysis. These patients have poorer outcomes than those who do not reocclude their vessels during thrombolysis. Platelet activation after exposure to thrombolytic agents has been postulated as a potential cause for this phenomenon, making a case for antiplatelet aggregating agents during thrombolysis. It is possible that some of the patients with apparent clinical improvement after intravenous rtPA who deteriorate subsequently might have persistent thrombus, as observed in our patient.

Factor V Leiden mutation is found in 4% to 6% of the US white population. This mutation is associated with a 3- to 6-fold increase in risks for venous thromboembolism, but there is no clear evidence for arterial thrombosis. This mutation is rare in black individuals of African descent. In a relatively large study of prothrombotic gene mutations, Berge et al found a small, nonsignificantly higher risk of early recurrent ischemic cerebrovascular events among patients who were carriers of the Factor V Leiden mutation. Botto et al found increased prevalence of at least one prothrombotic genotype among patients with patent foramen ovale and first-ever ischemic cerebrovascular event before the age of 55 years. In fact, a combination of Factor V Leiden mutation or prothrombin gene mutation and patent foramen ovale was associated with a 4.7-fold increased risk for ischemic stroke. Some earlier studies have failed to identify Factor V Leiden mutation as an independent risk factor for stroke.

In a pair-matched case–control study correlating the Factor V Leiden and prothrombin gene mutations in a cohort of 120 patients with ischemic stroke and 120 control subjects younger than 65 years of age, Eterovic et al observed a negative interaction of these mutations with clinical risk factors. In patients, but not in control subjects, the carriers of either mutation were mostly women and with fewer clinical risk factors for arterial ischemic events. More importantly, when both mutations were considered as a single coagulation deficit, their presence increased the likelihood of ischemic stroke, particularly among women, normotensive individuals, and those having normal cholesterol and triglyceride levels. These observations of the previously cited authors are relevant in this context because our patient did not have any apparent clinical risk factor.

In animal studies, Sampram et al found that the carotid arteries occluded within 60 minutes of injury in 97.3% of mice with Factor V Leiden mutation, homozygous occluding faster than heterozygous. Cooley et al also demonstrated a higher propensity for arterial occlusion in homozygous than in wild mice.

The authors consider that recurrent rethrombosis after thrombolytic therapy in the reported case could have been only augmented by the Factor V Leiden mutation. However, the favorable clinicoradiological outcome demonstrated in our patient might have been the result of aggressive and timely endovascular interventions.

Conclusions
Inherited thrombophilic states like Factor V Leiden mutation could contribute to reocclusion after endovascular interventions in stroke. Meticulous testing for thrombophilic mutations in selected cases like “cryptogenic stroke,” reocclusion after endovascular interventions, or stent thrombosis may be useful. Larger clinical studies to assess the frequency and etiology of thrombophilias in patients with arterial reocclusion are necessary.

Disclosures
None.

References


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Stroke. 2009;40:660-662; originally published online October 16, 2008;
doi: 10.1161/STROKEAHA.108.522771

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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