Intravenous Thrombolysis For Acute Ischemic Stroke in Fabry Disease

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Introduction: Fabry is a rare X-linked recessive genetic disease caused by α -galactosidase A deficiency. Cerebrovascular events occur in ~13% of patients, whereas stroke may be the presenting clinical manifestation. There are very limited case reports of tissue plasminogen activator administration for acute ischemic stroke in patients with Fabry disease.

Case report: A 46-year-old man presented with right-sided hemiparesis with a National Institutes of Health Stroke Scale score of 3. Brain computed tomography showed a hyperdense lesion resembling carvenous angioma. The patient received intravenous thrombolysis 265 minutes after symptom onset, with clinical improvement (discharge National Institutes of Health Stroke Scale score of 1). Brain magnetic resonance imaging disclosed acute thalamic infarction, cavernous angioma, and multiple cerebral microbleeds. The presence of skin angiokeratomas and cardiac hypertrophy prompted further positive investigation for Fabry disease (nondetectable α -galactosidase activity, excessively elevated lyso-Gb3, and pathogenic deletion in the *GLA* gene).

Conclusion: The present case supports the scarce data underscoring the safety of intravenous thrombolysis for acute ischemic stroke in Fabry disease patients even when cerebral microbleeds are present.

Key Words: Fabry disease, stroke, intravenous thrombolysis, cavernous angioma, cerebral microbleeds

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abry is a rare X-linked recessive genetic disease caused by α-galactosidase A (GLA) deficiency. It belongs to the lysosomal storage diseases resulting in the accumulation of globotriaosylceramide within various tissues and organs, including the eye, skin, brain, kidneys, peripheral nerves, and heart.¹ The disease was initially described by Fabry² and Anderson³ separately in 1898. Clinical manifestations typically begin during childhood or early adulthood (classic or earlyonset type); nevertheless, a wide spectrum of heterogenously progressive clinical phenotypes may be observed. Atypical variants (late-onset type) might present with symptoms at midlife or even later, and usually have isolated organ or system involvement.¹

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Ischemic stroke is a common complication of Fabry disease. Screening of 5978 high-risk cases for Fabry disease, presenting with stroke, found *GLA* mutations in 0.13% of male individuals and 0.14% of female individuals.⁴ Among patients diagnosed with Fabry disease, acute cerebrovascular events occur in ~13%, including 15% of male individuals, and 11.5% of female individuals, whereas, similarly to our case, stroke may commonly be the presenting clinical manifestation.^{5,6}

CASE REPORT

A 46-year-old man presented with acute-onset right-sided hemiparesis with a National Institutes of Health Stroke Scale of 3. His past medical history was insignificant other than current smoking (20 packs/ year). Concerning his family history, the patient's father had suffered a stroke at the age of 62 years. In the course of the initial clinical assessment, extensive skin angiokeratomas in the lower abdomen, the lateral thorax and abdomen, as well as the lips were noticed (Figs. 2A-C). When carefully examining the facial features, we observed periorbital fullness, bulbous nasal tip, broad alar base, prominent supraorbital ridges and nasal bridge, recessed forehead, bushy eyebrows, and full lips. Blood tests were unremarkable. Brain computed tomography (CT) showed a hyperdense lesion resembling cavernous angioma (Fig. 1A). Nevertheless, the patient received intravenous thrombolysis (IVT) 265 minutes after symptom onset, with significant clinical improvement (discharge National Institutes of Health Stroke Scale score of 1). The decision to administer IVT was based on the clinical judgment that was consistent with possible significant residual disability due to impaired dominant hand and lower limb functions, in a young professional driver who had been fully active before the stroke. Brain magnetic resonance imaging (MRI) disclosed a right frontal cavernous angioma, and an acute left thalamic infarction consistent with a lacunar-type ischemic stroke (Figs. 1B-D). Fluid-attenuated inversion recovery MRI sequences revealed chronic subtentorial ischemictype lesions, and susceptibility-weighted imaging sequences showed multiple (8 counts) deep cerebral microbleeds (CMBs), predominantly in the posterior fossa (Fig. 1E). Transthoracic echocardiography revealed concentric left ventricular hypertrophy, despite of the fact that the patient had no evidence of arterial hypertension (Fig. 2D). These findings raised suspicion of Fabry disease, which was investigated accordingly via fluorimetry, liquid chromatography-mass spectrometry, and, subsequently, DNA sequencing (Centogene AG, Rostock, Germany). The results verified nondetectable α -GLA activity, excessively elevated lyso-Gb3 levels (globotriaosylceramide level, 59.3 ng/mL; normal values, ≤ 1.8 ng/mL), and a pathogenic deletion [c.655del p.(Ile219Serfs*21)] in the GLA gene, confirming the diagnosis of Fabry disease.

DISCUSSION

Our patient had a typical multiorganic phenotype of Fabry disease with a late diagnosis that was prompted by a major clinical manifestation such as ischemic stroke. IVT with tissue plasminogen activator is the standard treatment for acute ischemic stroke (AIS).⁷ There are very limited case reports of tissue plasminogen activator administration for AIS in patients with Fabry disease.^{8,9} Our patient achieved significant clinical

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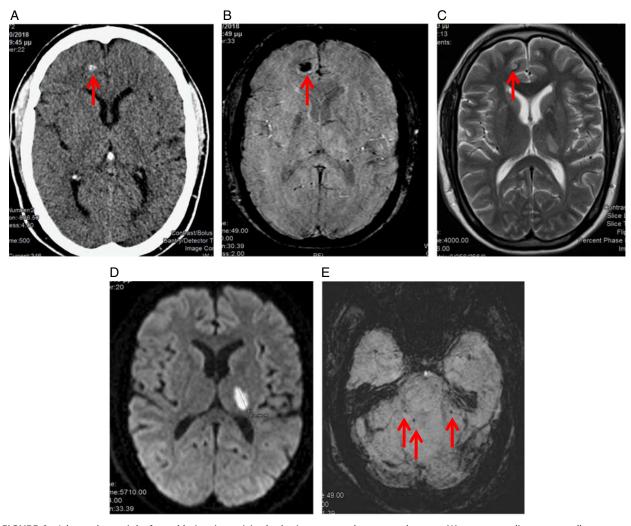


FIGURE 1. A hyperdense right frontal lesion (arrow) in the brain computed tomography scan (A), corresponding to a small cavernous angioma in the brain magnetic resonance imaging, as seen in susceptibility-weighted imaging (B) disclosing a hypointense lesion (arrow), and, in T2-weighted imaging showing a mixed intensity lesion (arrow) with a low-signal intensity rim (C). Brain magnetic resonance imaging diffusion-weighted imaging disclosing an acute left thalamic infarction (D). Susceptibility-weighted imaging showing multiple small cerebral microbleeds (arrows) in the cerebellum (E).

improvement and was discharged with minimal neurological deficits.

Admission CT scan revealed the incidental finding of a hyperintense lesion that corresponded to a cavernous angioma. Unruptured vascular malformations constitute a relative exclusion criterion for IVT, and, according to the most recent American Heart Association/American Stroke Association guidelines, IVT may be administrated to AIS patients with severe neurological deficits that justify undertaking the risk of a possible intracranial hemorrhagic complication (class IIb recommendation).¹⁰ Similarly, a recent consensus paper by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel suggested that the safety of IVT in patients with ischemic stroke and cavernous malformations is unclear (class III, level C).¹¹ A retrospective analysis of 350 IVT-treated patients reported the presence of cavernous malformations in 9 of them. Symptomatic intracerebral hemorrhage occurred in 1 patient and asymptomatic parenchymal hemorrhage in 2 patients. The rates of intracranial hemorrhage did not differ compared with 341 patients without cavernous malformations.¹² In our case, we chose to treat the patient, as the predicted final disability would most likely interfere significantly with his working ability and poststroke functionality, and as the time window for IVT was close to expiration (onset to the presentation time of 4 h). Moreover, the diagnosis of cavernous angioma solely by CT images was not definite.

CMBs on susceptibility-weighted imaging-MRI sequences are relatively common brain imaging findings of Fabry disease, present in up to 30% of patients, particularly in male individuals with concurrent T2 white matter hyperintensities and chronic kidney disease.^{13,14} CMBs increase the risk of hemorrhagic transformation after IVT. In particular, when > 10, the relative risk (RR) of symptomatic intracerebral hemorrhage compared with 0 to 10 CMBs is 12.1 (RR, 12.10; 95% confidence interval, 4.36-33.57; P < 0.001), and, compared with 1 to 10 CMBs, it is 7.01 (RR, 7.01; 95% confidence interval, 3.20-15.38; P < 0.001).¹⁵ Therefore, when CMBs are <10, as was in this case, IVT is reasonable (class IIa recommendation).¹⁰ Despite the concerns described above, our patient received IVT without complications.

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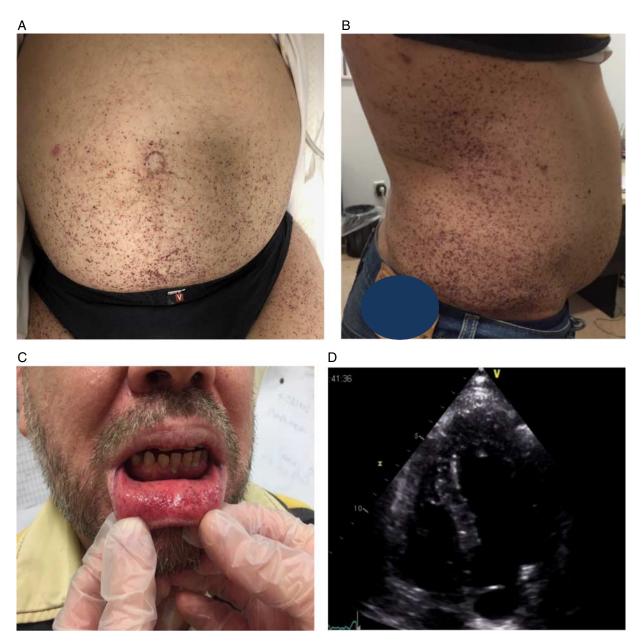


FIGURE 2. Lower and lateral abdomen, thigh, and lip angiokeratomas (A–C). Cardiac echocardiography revealing otherwise unexplained concentric left ventricular hypertrophy (D).

CONCLUSIONS

The present case, along with the 2 other published case reports,^{8,9} provide scarce data with regard to the safety of IVT for AIS in Fabry disease, even when CMBs are present. Additional publications in the form of case reports or series are needed to clarify the utility and safety of IVT in AIS attributed to Fabry disease, given the high comorbidity of renal failure and severe hypertension in these patients.

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