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Various Clinical Manifestations in a Heterozygous Fabry Disease Family: From Asymptomatic to Acute Ischemic Stroke with Intracranial Cerebral Artery Stenosis

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Dear Editor,

Fabry disease (FD) is a rare X-linked recessive lysosomal storage disorder characterized by decreased or absent activity of lysosomal α-galactosidase A (GLA), which results in accumulation of the glycolipid in various types of cell.[1] The estimated prevalence of FD at birth has ranged from 1:40,000 to 1:170,000, and its prevalence is about 4% in patients with cryptogenic stroke aged between 18 and 55 years.[2,3] Here we report a heterozygous FD family with various clinical manifestations from asymptomatic to acute ischemic stroke due to intracranial cerebral artery stenosis.

A previously healthy 36-year-old female (patient 1) was admitted with left hemiparesis. Her initial National Institutes of Health Stroke Scale score was 6 points, and her vital signs were stable except for elevated blood pressure at 149/100 mm Hg. Her own medical history was unremarkable, but her family history was significant for ischemic stroke in her grandfather, father, and uncle. Brain magnetic resonance imaging (MRI) revealed an acute infarction in the right middle cerebral artery (MCA) territory (Fig. 1A). Subsegmental narrowing of the right proximal MCA and anterior cerebral artery (ACA) was revealed by brain magnetic resonance angiography (MRA) (Fig. 1B) and digital subtraction angiography (DSA, Fig. 1C). GLA activity using a dried blood spot was within the normal range (3.16 μmol/h/L; normal range ≥1.32 μmol/h/L).

The 61-year-old mother of patient 1 (patient 2) took medication for hypertension and dyslipidemia. MRI and MRA detected multifocal hyperintense lesions in the white matter in fluid-attenuated inversion recovery imaging, while no remarkable stenosis was seen in brain MRA. Her GLA activity was within the normal range (5.94 μmol/h/L). The 33-year-old brother of patient 1 (patient 3) had no medical history. Brain MRI produced unremarkable findings, but brain MRA (Fig. 1D) and DSA (Fig. 1E and F) revealed segmental stenosis in the right MCA and a tortuous vertebrobasilar artery. His GLA activity was within the normal range (4.03 μmol/h/L).

The pedigrees of the family are shown in Fig. 1G. An ophthalmological examination, kidney ultrasonography, and peripheral nerve conduction study produced no remarkable findings in any patient. The molecular analysis of the *GLA* gene revealed a genotype of p.E66Q (c.G196C, p.Glu66Gln) on exon 2 (heterozygote in patients 1 and 2, and hemizygote in patient 3). After genetic testing we again performed fluorimetry, which revealed low GLA activity in patient 3 (9.8 μmol/L/h, normal range ≥15.3 μmol/L/h). Another genetic factor involved in vessel stenosis in young adults, the *ring finger protein 213* gene, is strongly associated with Moyamoya disease, but this was not detected in patients 1 and 3.

The present family exhibited various clinical phenotypes of heterozygous FD. The cerebral manifestations of FD can be classified as either large- or small-vessel disease.[4] Acute

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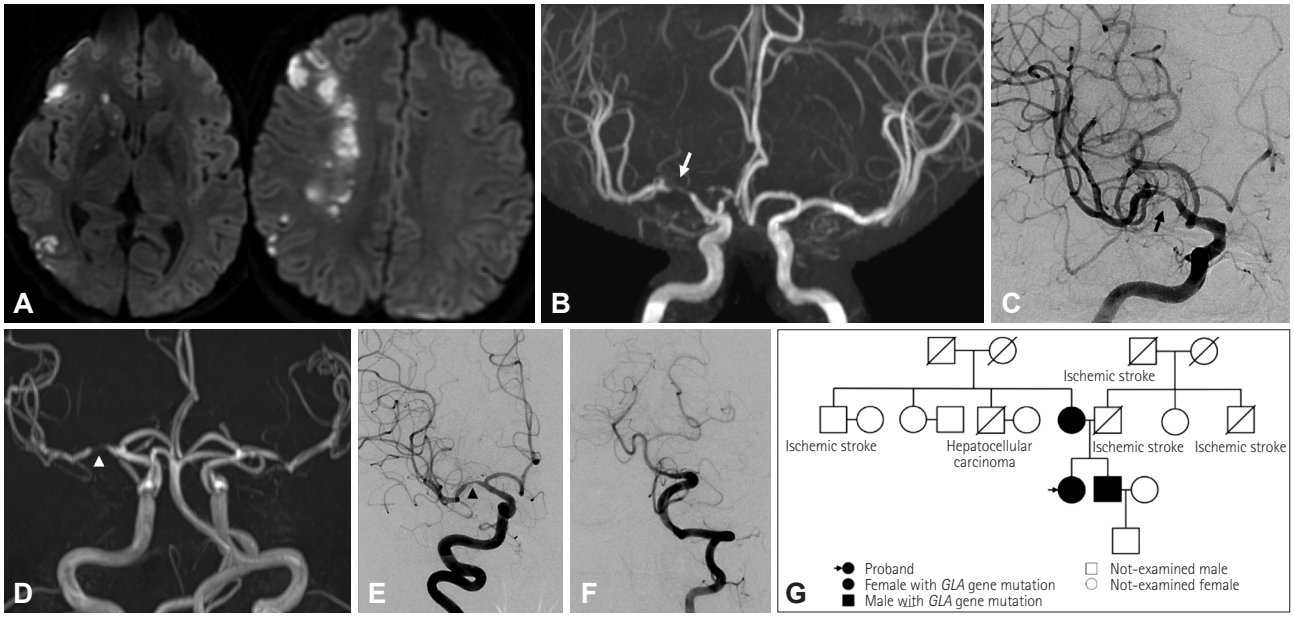

Fig. 1. Imaging studies and family pedigree of the patients. A: Diffusion-weighted imaging of patient 1 revealed a high-signal-intensity lesion in the right MCA territory involving the basal ganglia. B: Brain MRA revealed subsegmental stenosis (white arrow) in the right MCA and ACA. C: DSA also demonstrated severe stenosis (black arrow) in the right proximal MCA and ACA. D: Brain MRA revealed segmental stenosis (white arrowhead) in the right MCA of patient 3. E: DSA showed stenosis (black arrowhead) in the right MCA of patient 3. F: DSA showed the tortuous vertebrobasilar artery of patient 3. G: The family pedigree. ACA: anterior cerebral artery, DSA: digital subtraction angiography, MCA: middle cerebral artery, MRA: magnetic resonance angiography.

ischemic stroke due to large intracranial artery stenosis is a novel finding in FD because most ischemic strokes in FD occur within small vessels.[5]

The severity of FD manifestations in heterozygous female patients is complex due to the process of X chromosome inactivation (XCI).[4] Both random and skewed patterns of XCI have been reported in female heterozygous FD patients.[4] Patients with the random XCI pattern exhibit age-dependent worsening of clinical manifestations, whereas the skewed XCI pattern leads to the predominant expression of the wild-type *GLA* gene, and these patients exhibit an attenuated clinical phenotype in which disease progression is not correlated with age.[4]

More than 600 different mutations are known to exist in the *GLA* gene.[4] The p.E66Q *GLA* gene mutation detected in the present study is considered to be nonpathogenic based on its in vitro expression and prevalence in healthy alleles.[2] However, p.E66Q variants could be considered pathogenic because of the complexity of the *GLA* gene and gene–environment interactions.[2]

We have reported a case series involving a heterozygous FD family that revealed the various clinical expressions of FD, with ischemic stroke as the most-serious disease manifestation.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: all authors. Software: all authors. Supervision: all authors. Validation: all authors. Visualization: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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