Images in Cardiovascular Medicine

Fabry Disease that Phenocopies Hypertrophic Cardiomyopathy: a thorough Genetic ‘Detective’ Identifies the ‘Rogue’ Hidden in the GLA Gene

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A 59-year-old man with a history of hypertrophic cardiomyopathy, kidney transplantation, and unusual multifocal ischemic lesions in the cerebral white matter visited our hospital for resuscitated cardiac arrest. Electrocardiogram and 2D-echocardiography demonstrated concentric hypertrophy (left ventricular wall thickness 23–24mm) and left ventricular systolic dysfunction (ejection fraction 44%) (Figure 1 and Supplementary Videos 1–3). Endomyocardial biopsy showed enlarged, irregular-shaped, lipid-laden cardiomyocytes (Figure 2).¹⁾

Fabry disease (FD) is a rare X-linked inherited disease due to decreased lysosomal α -galactosidase A (GLA) activity. Considering the late-onset of clinical events, we strongly suspected a variant

Figure 1. Transthoracic echocardiography of the patient. There was marked concentric hypertrophy and systolic dysfunction. (A) Parasternal long axis view. (B) Parasternal short axis view at the level of papillary muscles. (C) Apical four chamber view. (D) 12-lead electrocardiogram consistent with left ventricular hypertrophy.

Figure 2. Histologic examination of the endomyocardial biopsy specimen. (A) Hematoxylin-and-eosin staining. (B) Masson's trichrome staining for myocardial fibrosis. (C) PAS staining for glycogen storage. The pathologic examination demonstrated perinucleolar vacuolization and hypertrophy of the cardiomyocyte with some interstitial fibrosis. The PAS staining revealed glycolipid storages accumulated within cardiomyocytes. PAS = Periodic acid-Schiff.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kwon S, Lee SP, Kim HK, Cho HJ, Sohn DW; Data curation: Kwon S, Lee SP, Park SS, Kim HK, Cho HJ, Seong MW, Sohn DW; Formal analysis: Kwon S, Lee SP, Kim BJ; Investigation: Kwon S, Lee SP, Park SS, Kim BJ, Cho HJ; Methodology: Kwon S, Lee SP, Park SS, Kim HK; Project administration: Lee SP; Supervision: Sohn DW; Validation: Lee SP, Park SS; Writing - original draft: Kwon S; Writing - review & editing: Kwon S, Lee SP.

Figure 3. Confirmation of the patient's *GLA* gene variation by Sanger sequencing and a pedigree. (A) The variant c.775C>T was identified at the exon 5 of the *GLA* gene of the patient. (B) Pedigree of the patient. The father had sudden cardiac death without a known cause. The mother of the patient had no significant medical history but refused genotyping. Among the siblings, only the 1st daughter agreed to the genetic test and was demonstrated to have the same mutation. However, her echocardiography was normal. In this case, Fabry disease may be not manifested because of the normal *GLA* produced by the other X chromosome. ICH = intracranial hemorrhage; SCD = sudden cardiac death.

form of FD and measured the patient's plasma GLA level and the enzyme activity. The plasma GLA level was 4.4 nmol/hr/mg protein (reference range=35–100 nmol/hr/mg protein) and the enzyme activity was 68.3% (reference range=85–95%). Both next-generation and Sanger sequencing of the *GLA* gene identified a novel mutation (c.775C>T [p.Pro259Ser]) at exon 5 (**Figure 3A**). The pedigree did not provide any more diagnostic clues (**Figure 3B**).

The mutation was not found in known public database of control subjects,²⁾ and a different mutation at the same amino acid residue had been reported before.³⁾ The genetic variation was located in a functionally critical domain and we found multiple computational evidences supporting the deleterious effect of the genetic variation (**Supplementary Table 1**). Combining these findings to pathogenicity criteria by the American College of Medical Genetics and Genomics,⁴⁾ the novel mutation c.775C>T (p.Pro259Ser) was considered to be likely pathogenic and we concluded the patient had a variant form of FD.

SUPPLEMENTARY MATERIALS

Supplementary Video 1

The parasternal long axis view of transthoracic echocardiography of the patient.

[Click here to view](#)

Supplementary Video 2

The parasternal short axis view at the level of papillary muscles of transthoracic echocardiography of the patient.

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Supplementary Video 3

The apical four chamber view of transthoracic echocardiography of the patient.

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Supplementary Table 1

The evaluation of evidence of pathogenicity of the patient's *GLA* gene mutation using the ACMG criteria⁴⁾

[Click here to view](#)

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