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Fabry Disease in a Female Patient due to a *de novo* Point Mutation at Position 691 of Exon 5

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Abstract
Fabry disease is an X-linked lysosomal disorder caused by deficiency of the lysosomal enzyme α-galactosidase A. We report on a 32-year-old female patient with an 8-year history of vascular lesions on the hips and periumbilical region and a presumed Fabry disease without positive family history. Ophthalmologic evaluation revealed whorl-like corneal opacities. Echocardiography revealed myxomatous degeneration and prolapse of the mitral valve. DNA analysis of the α-galactosidase A gene confirmed the diagnosis of Fabry disease, showing a *de novo* point mutation at position 691 of exon 5. The patient is now obtaining intravenous enzyme replacement therapy with agalsidase alfa and remains without drug-related reactions.

Key words: Fabry disease; α-galactosidase A; heterozygous

Introduction

Fabry disease (McKusick 301500) is an X-linked disorder of the glycosphingolipid metabolism resulting from deficient activity of the lysosomal enzyme α-galactosidase A. It leads to progressive accumulation of neutral glycospingolipids, especially globotriaosylceramide (ceramidetrihexoside), in endothelial, perithelial, and smooth muscle cells of blood vessels, epithelial cells of the cornea and kidney, cardiac myocytes, and ganglion cells of the autonomic nerve system. The estimated incidence of Fabry disease in Caucasians is 1 in 40.000 to 1 in 60.000 male live births [3]. Fabry disease in its classical form manifests in male individuals during early childhood with angiokeratoma corporis diffusum, hypo- or anhidrosis, acroparaesthesias, corneal opacity, and subsequent renal and cardiovascular involvement. The course of the disease is limited by development of end-stage dysfunction of kidney and heart, leading to lethal complications in the 4th to 5th decade in untreated cases. In general, heterozygous females present a milder form of the disease or are asymptomatic, but may be affected in the same manner as hemizygous males because of skewed X-chromosome inactivation (lyonisation).

We report on a female patient with a *de novo* mutation leading to Fabry disease with cardiac involvement.

Case Report

A 32-year-old female with an 8-year history of vascular lesions on the hips and periumbilical region and presumed Fabry disease was referred to our department for further evaluation. The suspicion of Fabry disease was raised 23 years ago, during a routine ophthalmologic examination revealing bilateral corneal opacities. The patient did not suffer from acroparaesthesias or sweating disturbances. No family history of Fabry disease was reported.

Physical examination did not reveal any apparent abnormalities except of the presence of multiple angiokeratomas in a grouped distribution on the hips (Fig. 1) and in the periumbilical region. Ophthalmologic evaluation revealed whorl-like corneal opacities. Routine laboratory parameters and levels for serum creatinine, creatinine clearance rate, and 24-hour protein excretion level were within normal range. Nerve conduction studies performed under standard conditions did not show any abnormalities. Echocardiography revealed myxomatous degeneration and prolapse of the mitral valve. No left ventricular hypertrophy was seen.

Paraffin-embedded skin sections showed the typical features of angiokeratoma. Frozen skin sections revealed accumulation of PAS-positive deposits within vascular endothelial cells.

Although α-galactosidase A activity in leukocytes of both parents was within normal range, it was significantly decreased in the patient (0.1444mU/mg, normal range 0.36 - 0.84mU/mg). DNA analysis of the α-galactosidase A gene revealed a point mutation at position 691 of exon 5 compared to wild type control (Fig. 2). This changed codon 231 for GAC coding for aspartate to AAC coding for asparagine (p.Asp231Asn). Molecular genetic analysis of the parents did not reveal the mutation described above.

A diagnosis of Fabry disease with cardiac involvement could be established. The patient is now obtaining intravenous enzyme replacement therapy with agalsidase alfa (Replagal®, Shire Human Genetic Therapies, Cambridge, USA) at a dose of 0.2 mg/kg body weight every two weeks, which has been demonstrated to have beneficial effects in female Fabry patients [1]. No drug-related infusion reactions have been observed so far.

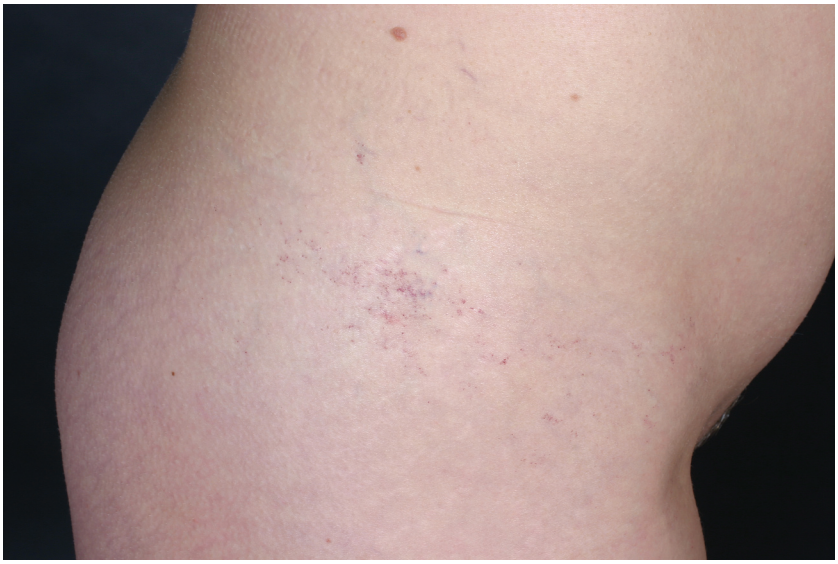

Fig. 1. Multiple angiokeratomas on the hip.

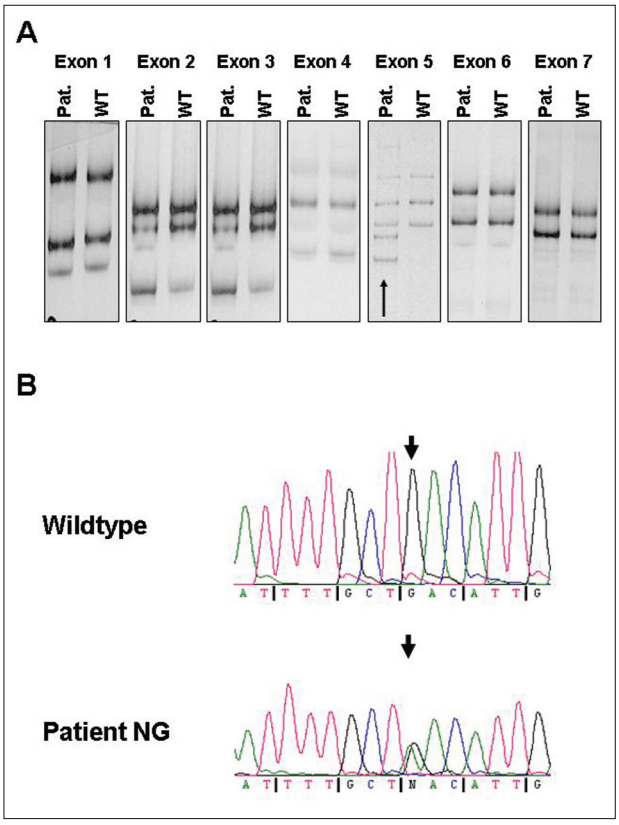

Fig. 2. DNA analysis of the α-galactosidase A gene of the patient revealed a point mutation at position 691 of exon 5 compared to wild type control.

Discussion

Fabry disease is a rare X-linked lysosomal storage disorder. The α-galactosidase A gene is located on the long arm of the X-chromosome (Xq22.1). More than 300 different mutations have been described so far, including missense and nonsense mutations as well as gene rearrangements (deletions, duplications). Most mutations occur as unique or private alleles [3]. Our case corresponds to the clinical picture of a heterozygous female with low enzymatic activity [2]. Enzyme replacement therapy was considered the best approach since cardiac involvement in heterozygous females with Fabry disease shows progression with age [2, 5]. The mutation found in our patient has been reported previously by Rodonnet-Vernhet et al. in a female monozygotic twin pair with discordant clinical expression of the disease [6]. This mutation leads to an amino acid substitution, which may influence the structure and/or function of the enzyme. Interestingly, the mutation was detected in our patient but not in her parents. Recently, Dobrovonly et al. reported a case of germline mosaicism in a healthy male whose both daughters suffered from a severe form of Fabry disease [4]. This possibility was not investigated in our case.

In conclusion, we suggest that a non-hereditary mutation of the α-galactosidase A gene is responsible for Fabry disease seen in our patient, manifesting with reduced enzyme activity, typical skin lesions, corneal opacities, and cardiac manifestations. This report emphasizes the importance of early diagnosis and start of enzyme replacement therapy to prevent irreversible vital organ damage that occurs during the course of the disease.

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