CASE REPORT

Dermatologic manifestations and neuropathic symptoms in women with Fabry disease

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Summary. Fabry disease (angiokeratoma corporis diffusum universale) is a rare, progressive, X-linked lysosomal storage disease. Deficiency of the α-galactosidase A (α-gal A) enzyme leads to accumulation of neutral glycosphingolipids within vascular endothelial lysosomes of various organs, including skin, kidneys, heart, and brain (1). We herein describe the case of a 30-year-old female presenting two classic signs of Fabry disease, angiokeratomas and episodic acroparesthesias, in the absence of other clinical manifestations. An haplotype corresponding to the combination of three different nucleotide polymorphic variants (g. 7192-7198del5+ g. 10115A>G + g. 10956 C>T) at the heterozygous state, was identified (2).

Key words: Fabry Disease, neuropathy, angiokeratoma

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease, caused by mutations of the GLA gene, which is located on chromosome Xq22.1 and encodes the lysosomal enzyme α-galactosidase A (α-gal A) (3). Deficient α-gal A activity results in impaired biodegradation of glycosphingolipids, which accumulate together with α-galactosyl breakdown products within the lysosomes of several organs. Globotriaosylceramide (Gb3) is the predominant lipid found in kidney epithelial cells, cardiac cells, valvular fibrocytes, neurons, and vascular endothelial, perithelial, and smooth muscle cells of patients affected by FD. These deposits are believed to cause selective functional alterations in specialized cells, ultimately impacting on the global performance of different organ systems (4). Because of the X-linked model of inheritance, it has been postulated that only males are affected whereas heterozygous females are asymptomatic. In male patients with decreased or absent α-Gal A activity, the onset of the disease occurs in childhood or adolescence and is characterized by severe acroparesthesias, angio-keratomas, corneal opacities, and hypohidrosis. Over time, typically during the fourth and fifth decades of life, left ventricular hypertrophy and coronary microvascular dysfunction, nephropathy with kidney failure, cerebral micro- and macro-vasculopathy with early dementia, may occur.

However, recent studies have shown that females may show characteristic signs of FD, and many of them are severely affected. The observed phenotypic heterogeneity in females is thought to be due to lyonization, a process by which one of the two copies of the X chromosome is inactivated (5), so that heterozygous females are a 'mosaic' of normal and mutant cells in variable proportions. The clinical spectrum in females suffering from FD ranges from a seemingly asymptomatic course to the classic severe phenotype observed in males, with a variety of intermediate clinical presentations (6-7-8). The assessment of α-Gal-A activity in leukocytes or fibroblasts is an efficient and powerful method for the diagnosis of FD in males. However, for heterozygous female patients, the value of enzymatic activity is not very indicative, since a clear relationship between this parameter and the

clinical signs of the disease has not been established women. Because of the random inactivation of the X chromosome, patients with severe clinical manifestations may have normal α-gal A blood activity, pointing to the importance of genetic testing for the diagnosis of FD in women (9).

The incidence of FD in males has been estimated to be 1:50,000, whereas the incidence in the general population varies from approximately 1:117,000 to 1:833,000 (10-11). However, the true prevalence of FD may be higher.

We report the case of a 30-years-old female patient who showed a mild form of FD in the absence of multisystemic involvement. Molecular analysis revealed GLA polymorphisms in non coding regions of the gene.

Case report

In January 2010, a 30-year-old Caucasian female came to our outpatient practice for the evaluation of chronic skin lesions. Small, raised, reddish-purple maculopapules were distributed on the abdomen, buttocks, lower trunk and limbs. She reported that the skin lesions appeared during adolescence and increased in number and size with age (Fig. 1). The patient, who was born from unrelated parents after an uncomplicated C-section delivery, did not show dysmorphic features. There was no known family history of hereditary diseases or skin lesions.
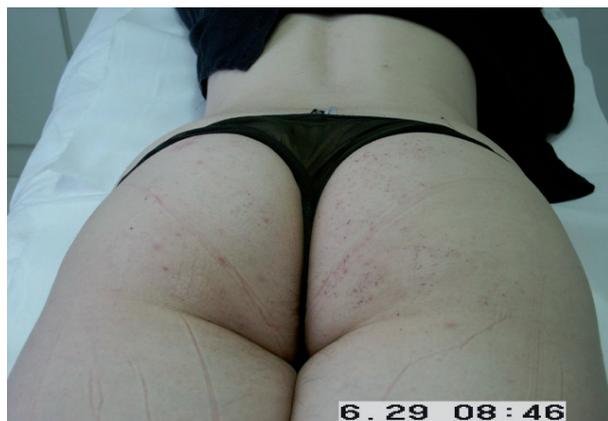
The patient suffered from palpitations and reported sporadic episodes of acroparesthesia, described as a pin prick sensation underneath the toes and in the legs. This neuropatic pain did not appear to be related to high ambient temperature or fever, although the patient reported low tolerance to hot weather. The patient reported also the presence of persistent microematuria which was not accompanied by proteinuria. The clinical diagnosis of angiokeratomas was confirmed by the histopathologic examination of a bioptic specimen obtained from a small papule in the left side of the back. Moderate hyperkeratosis was coupled with dilated blood vessels filled with erythrocytes in the epidermis (Fig. 2). In the upper dermis, extremely dilated vessels were present. Some of the vessels were surrounded by epithelial sprouts and a moderate diffuse lymphocytic infiltrate was observed. Collectively, these findings were consistent with a diagnosis of FD.

The patient underwent a thorough clinical evaluation. Routine hematological tests were normal including serum creatinine levels, 0,8 mg/dl. Electrocardiographic and echocardiographic analyses showed normal cardiac chamber size and wall thickness. Furthermore, the patient had normal blood pressure (120/60 mmHg). On neurological examination, ankle reflex, tendon reflexes, and muscle strength were normal. Moreover, no abnormalities were found by brain magnetic resonance imaging. There were no aneurysmal dilatations of the conjunctival vessels or diffuse corneal opacities, typical of cornea verticillata.

Figure 1. ??????????

Figure 2. ?????

The biochemical analysis of the leukocyte α-Gal A activity was not performed because of the lack of relevance of this parameter for FD diagnosis in females. To determine whether GLA was mutated, polymerase chain reaction (PCR) sequencing was performed on DNA extracted from peripheral blood cells. The analysis of the DNA sequence for exon and exon/intron boundaries of the GLA gene revealed the presence of GLA polymorphic nucleotidic variants, g. 7192-7198del5+ g. 10115A>G + g. 10956 C>T, at heterozygous state. As specifically Due to patient›s personal reason, genetic counseling and evaluation of other family members were not performed, although her brother showed facial angiokeratomas and a positive history for kidney neoplasm.

A 1064 nm long-pulsed Nd:YAG laser was used to treat the cutaneous lesions. The patients received 3 laser treatment sessions at an interval of 2 months. Nd:YAG laser treatment yielded successful results in the management of our patient›s angiokeratomas following 3 application sessions. We suggest that a long-pulsed Nd:YAG laser is a safe and effective method for the treatment of angiokeratomas in Fabry disease.

Discussion

Fabry disease is a rare X-linked lysosomal storage disease caused by α-gal A enzyme deficiency. In X-linked diseases, heterozygous females may be symptomatic, probably as a consequence of skewed X-chromosome inactivation, which results in a higher percentage of the X-chromosome bearing the mutant gene being expressed in the cells of the target tissue. Such variability in symptom severity is characteristic of X-linked heterozygotes (12) and should be taken into account when assessing and diagnosing potential patients. Heterozygotes may display the entire spectrum of clinical manifestations of FD, including pain, orthostatic hypotension, angiokeratoma, ocular abnormalities, cochleovestibular involvement, gastrointestinal symptoms and respiratory problems (13-18). A high percentage of females develop damages of the heart, brain and, more rarely, kidneys, usually about a decade later than males (19). Of the 1077 enrolled females in the Fabry Registry®, 69.4% had symptoms

and signs of FD. The median age at symptom onset in females was 13 years, and 20% experienced major cerebrovascular, cardiac, or renal events, at a median age of 46 years (19). Moreover, female patients with FD have a significant risk for major organ involvement and decreased quality of life, and they should be regularly monitored (13).

In this paper, we report the case of a 30 year-old female patient who presented the classical skin signs of angiokeratomas and mild small-fiber neuropathy, in the absence of other manifestations of Fabry disease. A genetic survey found, in heterozygosis, intronic benign polymorphic variants as 7192-7198del5, g.10115A>G (IVS4-16A>G), g.10956C>T (IVS6-22C>T) in the GLA gene, combined in a single haplotype. These mutations do not correlate with significant variations of α-Gal-A activity and they are not likely to have major phenotypic effects, although their presence does not completely rule out the possibility of mild or moderate effects that could be detected in larger cohorts of subjects. On this basis, it has been proposed that the detection of polymorphic haplotype combinations, including less frequent GLA polymorphic alleles, in the absence of GLA sequence variations should be considered as a coincidental finding, not relevant for FD diagnosis (2). However, it has to be taken into account that noncoding regions are not routinely evaluated when sequencing the GLA gene. Thus, we believe that the occurence of intronic disease-causing lesions should prompt a deeper molecular screening and a careful clinical and instrumental evaluation of subjects carrying these genetic abnormalities. This approach may lead to confirm diagnosis of FD in a larger number of patients, thus providing a more realistic estimate of the prevalence of FD in the general population.

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