

Prevalence of dermatologic manifestations in patients with Fabry disease in Argentina

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Abstract

Anderson-Fabry disease is an X-linked lysosomal storage disorder caused by deficient α -galactosidase A activity.

Objective. To record the prevalence of dermatologic manifestations in patients with Fabry disease in Argentina.

Methods. We studied 40 males and 40 females with Fabry disease. Diagnosis was confirmed by blood enzyme assays and genetic tests.

Results. Angiokeratomas appeared in 82 percent of male adults, and in 34 percent of female adults. Most frequent locations were, in males the periumbilical area, scrotum and penis, buttocks and lips; in females the chest, periumbilical region, and fingers.

Telangiectasias on oral mucosa were present in 50 percent of hemizygous and 25 percent of heterozygous patients. We found hypohydrosis in 75 percent of adult males, 31 percent of adult females, and 18 percent of female children. We searched for correlations between systemic findings and the presence of angiokeratomas.

Conclusion. Angiokeratomas were the second most frequent manifestation found in our patients. Dermatologic manifestations were usually present in adult hemizygous patients, and less frequently in females and children. We found positive correlation between angiokeratomas and other early signs and symptoms of Fabry disease; therefore, we emphasize the role of dermatologists in early diagnosis of this disease (Dermatol Argent 2008;14(5):362-366).

Key words: Fabry disease; angiokeratoma.

Introduction

Fabry disease (FD) is a rare hereditary lysosomal storage disorder caused by partial or absolute deficiency of the α -galactosidase A enzyme, with the resulting accumulation of glycosphingolipids (particularly globotriaosylceramide or Gb3) in visceral tissues and vascular endothelium of the whole body. Incidence is estimated in 1:117,000 live births, and in 1:40,000 men.¹

It is an X-linked recessive inherited disease; therefore, the sons inheriting the gene will be affected by the disease, the daughters will be carriers, but may also be variably affected by random inactivation of the X chromosome. Parents with the disease do not transmit the defective gene to their sons, but they do transmit it to their daughters.²

Main weakening manifestations of Fabry disease are the result of progressive accumulation of globotriaosylceramide (Gb3) in vascular endothelium, especially in kidney, heart, and brain; severe multiorgan damage leading to death around 50 years of age in hemizygous patients, and around 60 years in heterozygous patients.^{3,4}

Although clinical onset occurs in childhood, the appearance of the disease may be subtle, and its signs and symptoms are often set aside as simulation, or attributed to other disorders, such as rheumatic fever, erythromelalgia, neurosis, Raynaud, polyneuropathy, multiple sclerosis, acute appendicitis, lupus, petechiae, or "growth pains," among others.^{1,5}

Reception date: 21/7/08 | **Approval date:** 7/8/08

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The simplest recognizable clinical characteristics are angiokeratomas, which are red to violaceous, papular lesions that do not disappear upon pressure, generally grouped in the buttock, and umbilical areas, the thighs and genitals (typical bathing suit distribution), and may extend to the whole tegument. Although not pathognomonic of this disease, angiokeratomas and telangiectasias are part of cutaneous manifestations, or “FD rash,” according to some authors.^{3,15}

Impairment of sweating ability in these patients produces xeroderma with intolerance to heat and exercise; 50 percent of cases may also have reduced production of tears and saliva.⁶

At ophthalmological level, slit lamp examination evidences cornea verticillata; and posterior cataracts and vascular damage may also be seen by ocular fundus. Gastrointestinal manifestations may occur as episodic diarrhea, pain, and postprandial feeling of fullness, early satiation, weight loss, nausea, and vomiting. Most Fabry disease patients develop proteinuria in late adolescence, which progresses to isosthenuria and produces tubule function alterations. Renal complications announce the terminal stage of the disease and are the most frequent cause of death in homozygous patients. Cardiac involvement is variable and its seriousness increases with age.⁷

Until 4 years ago, the existing treatment for this disease was symptomatic; dialysis or renal transplant could extend life, but although the transplanted kidneys remained free from the disease, damage to other systems continued in progress, especially in the brain and the cardiovascular system. In mid-2001, two groups of investigators published randomized and placebo-controlled assays evidencing that in Fabry disease enzymatic replacement may revert the main pathological consequences.⁸⁻¹⁰ These studies show statistically significant reduction of the Gb3 content in blood and urine, with improvement of renal, cardiac, liver, and skin histopathology, where Gb3 lysosomal inclusions decreased.

Objective

To document prevalence of dermatological manifestations in Fabry disease patients in Argentina, and their correlation with systemic signs and symptoms.

Material and methods

For 4 years (2003-2007), 80 patients with EF from five provinces of the Argentine Republic were studied: 40 hemizygous males, and 40 heterozygous females, distributed in 6 different families; included were 11 males and 5 females under 15 years of age. Mean age of diagnosis in males was 26.9 years (range: 6-51 years), and in females, 31.4 years (range: 5-70 years).

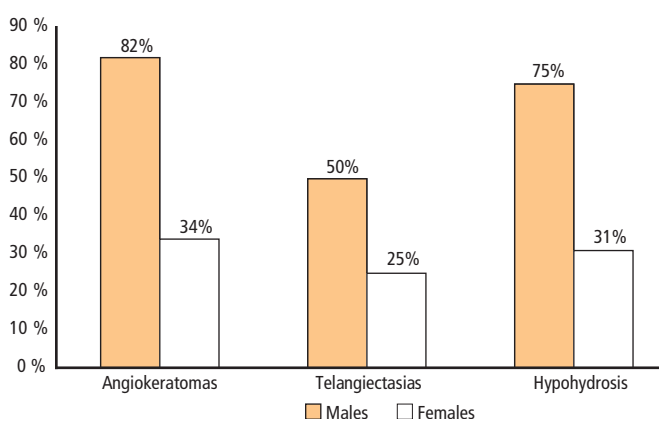
Diagnosis was confirmed in all patients through blood enzyme tests of filter paper (adaptation of the method developed by Chamoles) and/or genetic tests, if necessary, with dry drops of blood on FTA® filter paper, and polymerase chain reaction.

Patients were assessed by complete dermatologic, neurologic, ophthalmologic, cardiologic, and clinical examination performed by physicians from the Association for the Study and Diffusion of Fabry Disease and Lysosomal Diseases in Argentina (*Asociación de Estudios y Difusión de Enfermedad de Fabry y Enfermedades Lisosomales en Argentina*, AADELFA), a multidisciplinary group created for the diffusion, assessment and treatment of lysosomal diseases.

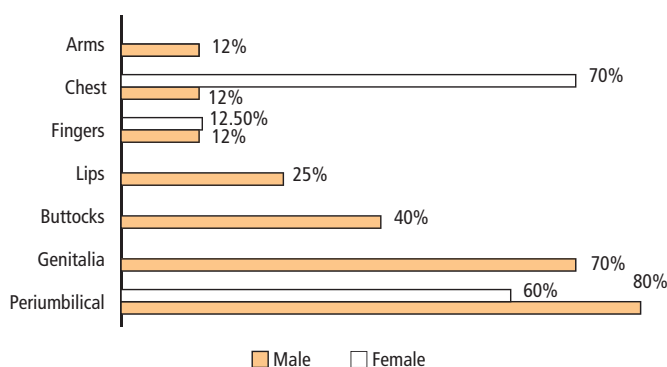
Results

Cutaneous manifestations were found in 47 percent of the cases (**Graph 1**). There were angiokeratomas in 82 percent of adult males (24/29), and 34 percent (12/35) of adult females. Most frequent location in males was the periumbilical area (80 percent of the cases), scrotum and penis (70 percent), buttocks (40 percent), lips (25 percent), fingers, chest and arms (12 percent of the cases), with lesions tending to join by regions (**Figures 1, 2, and 3**). In women, the angiokeratomas were smaller and more disseminated, and more frequent on the chest (70 percent of the cases), periumbilical area (60 percent) and fingers (12.5 percent) (**Graph 2**).

There were telangiectasias in oral mucosa in 50 percent of hemizygous patients and in 25 percent of heterozygous patients. Patients' perception of their sweating capacity and heat tol-



Graph 1. Prevalence of dermatological manifestations in Fabry disease patients in Argentina.



Graph 2. Distribution of angiokeratomas.

erance were assessed by medical history. There were hypohydrosis and heat intolerance in 75 percent (22/29) of adults, 31 percent of female adults (11/35), and 18 percent of girls (2/5).

In seeking correlation between the presence of angiokeratomas and systemic findings (**Graph 3**), the findings were acroparesthesias in 94.7 percent of patients with angiokeratomas (37/39), hypohydrosis in 94.7 percent (37/39), cornea verticillata in 87 percent (33/39), proteinuria in 82 percent (31/39), left ventricular hypertrophy in 33 percent (13/39), and renal failure in hemodialysis in 20.51 percent (8/39).

Discussion

Fabry disease is a rare disorder with various and non-specific signs and symptoms, described for the first time independently by two dermatologists, William Anderson and Johannes Fabry, en 1898.^{11,12}

The study includes 80 patients with Fabry disease from 6 different families in Argentina; noteworthy are the 2 index families accounting for 70 percent of total cases, who were diagnosed by dermatologists. Genetic studies revealed that each family had its own mutation, in all cases point mutations; thus, four new mutations were reported in the literature.¹³ In all cases, the classical phenotype was found, with systemic manifestations similar to those found in the literature.

The most frequent manifestations in our patients were the neurological symptoms: acroparesthesias and pain crisis, found in 86 percent of males and in 42 percent of females, as well as cornea verticillata as distinctive sign found in 83.3 percent of males and in 63 percent of females.

Dermatologic manifestations usually appeared in hemizygous patients, and with less frequency in women and children. As reported in the literature, angiokeratomas were the second most frequent sign found in our patients (83 percent en males and 34 percent in females).

Female patients had isolated and discrete angiokeratomas, and their location on the chest and fingers was more frequent than expected. Telangiectasias were present mostly in males; and hypohydrosis and heat intolerance appeared in 75 percent of adult males, and in 32 percent females, including two girls. There was a positive correlation between the presence of angiokeratomas and other early signs and symptoms of Fabry disease, such as acroparesthesias, cornea verticillata, and proteinuria.

In comparing these data with those published by the

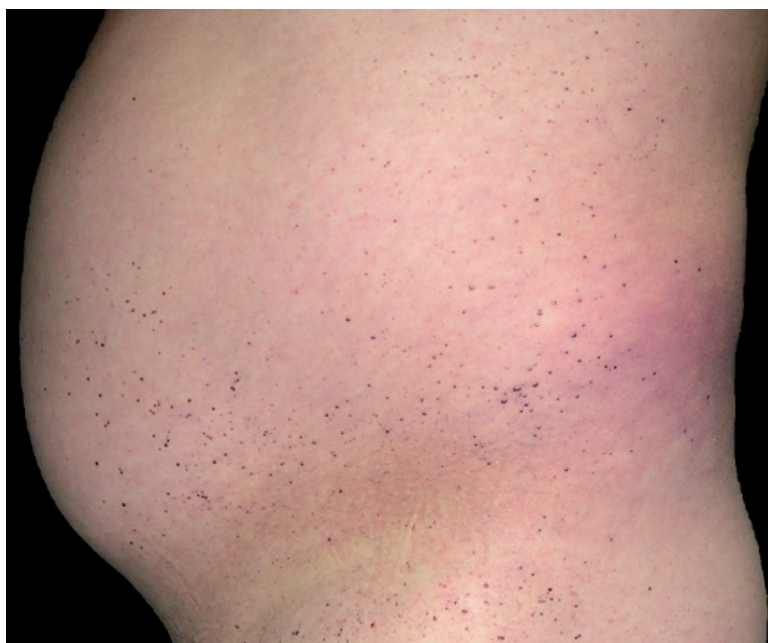


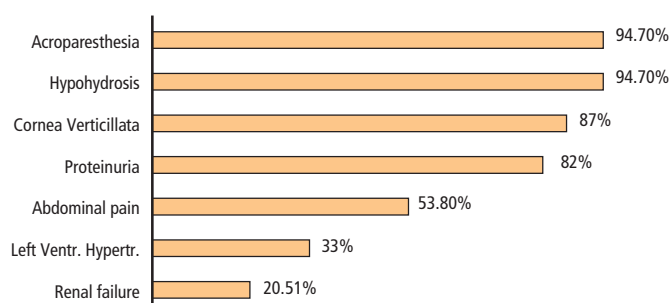
Figure 1. Angiokeratomas with typical "bathing suit" distribution.



Figure 2. Angiokeratomas and telangiectasias in lip mucosa.



Figure 3. Angiokeratomas in scrotum and penis.



Graph 3. Correlation between the presence of angiokeratomas and systemic findings.

Fabry Outcome Survey (FOS), our series found more frequently angiokeratomas, telangiectasias, and hypohydrosis in adult hemizygous patients and telangiectasias and hypohydrosis in females. In the FOS series, they found greater correlation with neurological, cardiologic, gastrointestinal, and otolaryngology alterations in patients with angiokeratomas.¹⁴

Conclusion

Fabry disease is a rare disorder, often underdiagnosed, where due to its variable clinical appearance diagnosis is often underestimated or delayed. In the large series of cases reported, the early presence of dermatological manifestations stands out. Therefore, we emphasize the dermatologist's role in the early diagnosis of this pathology for the possibility of offering patients an effective treatment that prevents progression and reverts the multiorganic dysfunction leading to a premature death.

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