Fabry Disease

A Study of 6 Hemizygous Men and 5 Heterozygous Women With Emphasis on Dermatologic Manifestations

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Objective: To determine the significance of the dermatologic and systemic abnormalities found in 11 patients with Fabry disease (FD) which is an X-linked lysosomal storage disorder caused by the partial or complete deficiency of the α-galactosidase A enzyme. This defect leads to the accumulation of uncleaved glycosphingolipids throughout vascular endothelium and visceral tissues.

Design: Case series.

Setting: Pediatric Dermatology Division, Ramos Mejía Hospital (primary care center) and Laboratory of Neurochemistry (referral center for metabolic diseases).

Patients: Eleven patients with FD were studied: 6 hemizygous men (mean age, 23.0 years) and 5 heterozygous women (mean age, 49.4 years).

Results: Mucocutaneous angiokeratomas (AKs) were found in 5 (83%) of 6 hemizygotes and 4 (80%) of 5 heterozygotes. The AKs appeared at an average age of 13 years, affecting predominantly genitalia, back, elbows, and other frequently traumatized areas. All the hemizygotes and none of the heterozygotes suffered from hypohidrosis. Angiokeratomas on the trunk and oral mucosa without sweat abnormalities were detected in 80% of heterozygous women. All hemizygotic men presented with acral pain in childhood.

Conclusion: We emphasize the value of early recognition of AKs and hypohidrosis as diagnostic clues to FD, a severe and progressive disorder.

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Anderson-Fabry disease, also known as Fabry disease (FD) or angiokeratoma corporis diffusum universale, was described independently by 2 dermatologists in 1898. Fabry disease is an uncommon X-linked recessive disease caused by deficient activity of the lysosomal enzyme α-galactosidase (α-gal) A. As a result of the enzyme deficiency, neutral sphingolipids accumulate, particularly in the vascular endothelium, leading to ischemia and infarction, especially of the kidney, heart, and brain. Inheritance of the abnormal gene among whites (resulting in a hemizygous boy or a heterozygous girl) has been estimated to occur once in every 117,000 live births.

Fabry disease is difficult to diagnose because of its heterogeneous signs and symptoms. In male patients with the classic phenotype, the onset of symptoms occurs in childhood or adolescence with chronic paresthesias and episodes of severe acral and/or abdominal pain (Fabry crisis), heat intolerance, lack of sweating, and angio-keratomas (AKs). In the absence of a family history, the diagnosis is generally made later, when the clinician is faced with end-stage organ damage. Renal failure combined with cardiac and cerebrovascular disease lead to early mortality. Milder forms of the disease, which present later in life and primarily affect the kidney or the cardiovascular system, are known as renal, cardiac, or intermediate variants of FD.

Clinical manifestations in female carriers range from asymptomatic to full-blown disease as severe as that in affected male patients. Asymptomatic corneal dystrophy is present in about 70% of carriers, which is useful for heterozygote detection. Approximately 30% of women have AKs and fewer than 10% have neuropathic pain. A recent study of obligate female carriers found significant disease manifestations in 20 of 60 women. Another study performed on 20 carriers of FD...
showed that each woman had some symptom of this storage disease, although symptom severity varied. Therefore, FD could be considered a storage disease transmitted as an X-linked–dominant and not an X-linked–recessive disease.14,15

Diagnosis in hemizygous individuals is based on the detection of low activity of α-gal A in plasma, leukocytes, cultured skin fibroblasts, or, as more recently noted, in dried blood spots on filter paper.16 Owing to random X-chromosomal inactivation, enzymatic detection of carriers may be inconclusive (enzyme levels similar to those in the general population). Therefore, detection of specific family mutation in the α-gal gene must be demonstrated.7,17

The α-gal A gene is located in the long arm of the X chromosome, locus Xq22.1. The defect that causes FD is very heterogeneous.18 To date, more than 300 mutations have been recognized.19 The degree of genotype-phenotype correlation in FD remains controversial. Thus, within families, the same mutation may cause different phenotypes.5 Most families have “private” mutations, that is, mutations found only in that particular family.16 Although it is important to investigate family history when FD is suspected, de novo mutations have been documented.20 Thus, absence of family history does not exclude the diagnosis of FD. We report herein the dermatologic and systemic findings of 6 hemizygous men and 5 obligate carrier women with classic FD.

### METHODS

We studied 11 patients with FD: 6 hemizygous men aged 19 to 32 years (average age, 23.0 years) and 5 obligate carrier women, aged 45 to 56 years (average age, 49.9 years). They belong to 4 different families: 2 brothers and their mother, 2 cousins and their mothers (sisters), and another 2 men and their respective mothers. The diagnosis of all heterozygotes was made after discovery of their son’s disease. Findings were negative in other family members screened for FD.

### Table 1. Cutaneous Findings in Hemizygous Men

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>23</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age at pain onset, y</td>
<td>5-6</td>
<td>8</td>
<td>5-6</td>
<td>5-6</td>
<td>5-6</td>
<td></td>
</tr>
<tr>
<td>Age at AK onset, y</td>
<td>13</td>
<td>7</td>
<td>15</td>
<td>13-14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>15</td>
<td>11</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Delay in diagnosis, y</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>AK initial site</td>
<td>Genitalia</td>
<td>Genitalia, elbow, back</td>
<td>Genitalia, elbow</td>
<td>Genitalia, elbow, waist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AK skin topography</td>
<td>Genitalia, elbow, limbs</td>
<td>. . .</td>
<td>Genitalia, elbow</td>
<td>Genitalia, elbow, waist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AK of oral mucosa</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Body hair density anomalies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Hypohidrosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>α-Gal activity in leukocytes*</td>
<td>1.9</td>
<td>1.1</td>
<td>0.6</td>
<td>1.2</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Plasma Gb3 level,† µg/mL</td>
<td>14.8</td>
<td>10.2</td>
<td>15.9</td>
<td>19.7</td>
<td>11.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AK, angiokeratoma; gal, galactosidase; Gb3, globotriaosylceramide; ellipses, no AK present; question marks, not remembered or not known.

*Measured in nanomoles per hour per milligram of protein (normal, 30.5-57.7 nm/h per milligram of protein).

†Normal, less than 6.5 µg/mL.

### Table 2. Cutaneous Findings in Heterozygous Women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49</td>
<td>49</td>
<td>48</td>
<td>45</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Skin AK</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Oral mucosal AK</td>
<td>No</td>
<td>No</td>
<td>Lips</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Abnormalities of sweating</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Body hair density anomalies</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>α-Gal activity in leukocytes*</td>
<td>20.8</td>
<td>33.8</td>
<td>14.1</td>
<td>15.9</td>
<td>15.6</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AK, angiokeratoma; gal, galactosidase.

*Measured in nanomoles per hour per milligram of protein (normal, 30.5-57.7 nm/h per milligram of protein).
raphy), and nephrologic (renal function testing, 24-hour microalbuminuria analysis, and renal echography). The skin biopsy specimens of 1 hemizygous man and one woman carrier were studied by electron microscopy. Mutation analyses were performed on all patients.

**RESULTS**

**HEMIZYGOUS MEN**

The earliest symptom was acral pain, and the earliest sign was the appearance of AKs. All 6 hemizygous patients had acral pain; the average age of onset was 6 years. Only 3 of 5 patients who had AKs could specify the age of onset (mean age of onset, 13.5 years). The average delay from the appearance of initial symptoms to FD diagnosis was 10.8 years.

Angiokeratomas were present in 5 of 6 hemizygous patients. They appeared initially on genitalia (3 of 5 patients) (**Figure 1**) and on the waist (1 of 4). Angiokeratomas were seen most often in a “bathing trunk pattern” and on elbows (5 of 5 patients), waist (3 of 5), extensor surfaces of arms (1 of 5) (**Figure 2**), back (1 of 5), and fingers (1 of 5). We stress the predominance of AKs in areas commonly exposed to trauma. Angiokeratomas involving lips (semincuseum and mucosa) were seen in 3 of 5 patients. Between 50 and 75 isolated AKs were found in 4 of 5 patients. The older hemizygous patient presented with more than 100 AKs distributed over the body. The morphologic characteristics of skin lesions varied from punctate angiectases to 1- to 10-mm red to black papules and plaques with verrucous surface (**Figure 3**). All mucosal lesions consisted of punctate macular angiectases. Generalized hypohidrosis with heat intolerance was present in 6 of 6 patients. None of these patients had xerostomia, but detailed sialometric studies were not performed. Alterations in hair density were not detected in this population. Therefore, in our series, 83% of men had AKs, and 100% had hypohidrosis.

**HETEROZYGOUS WOMEN**

Isolated cutaneous AKs (2 lesions in each patient) were present in 2 of 5 women. Two other heterozygous patients showed multiple macular angiectases affecting the lips (5 to 10 lesions), both mucosal and semimucosal surfaces. The
age of presentation of skin abnormalities was unknown. None of the 5 carrier women described either sweating abnormalities or xerostomia. Hair density abnormalities were not present in this heterozygous population.

HEMIZYGOUS MEN AND HETEROZYGOUS WOMEN

Electron microscopy of skin biopsy specimens showed estromal cells in hemizygous tissue (Figure 4) and endothelial and smooth muscle cells in heterozygous tissue (Figure 5) containing membrane-bound inclusions with a lamellar structure. Mutation analysis found that patient 6 and his mother had a complex deletion FS159 Stop in exon 3. This mutation causes a severe abnormality in the α-gal A structure. All the other patients and their mothers shared the same mutation at exon 7 (1244 T → C) that produces a substitution of leucine for proline at residue 413.

The dermatologic and systemic findings in our patients are summarized in Tables 1 and 2 and Table 3. Figure 6 shows vascular conjunctival tortuosity in 1 hemizygote.

### Table 3. Clinical Manifestations in Hemizygous and Heterozygous Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hemizygous</th>
<th>Heterozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>23.8 (19-32)</td>
<td>49.9 (45-56)</td>
</tr>
<tr>
<td>α-Gal activity in leukocytes (range)†</td>
<td>0.6-1.9</td>
<td>14.1-33.8</td>
</tr>
<tr>
<td>Plasma Gb3 level (range)‡</td>
<td>7.8-19.7</td>
<td>ND</td>
</tr>
<tr>
<td>Facial dysmorphism</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pain/acroparesthesias</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Salivary gland dysfunction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular tortuosity in conjunctiva</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vascular tortuosity in retina</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Corneal opacities/dystrophy</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Lens opacities/Fabry cataract</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal echocardiography</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal electrocardiography</td>
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<td>3</td>
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<tr>
<td>CNS involvement</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal crisis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AK, angiokeratoma; CNS, central nervous system; gal, galactosidase; Gb3, globotriaosylceramide; ND, not done.  
†Unless otherwise indicated, data are given as number of patients.
‡Measured in nanomoles per hour per milligram of protein (normal, 30.5-57.7).
†Normal, less than 6.5 µg/mL.

COMMENT

The enzymatic defect in FD leads to the accumulation of uncleaved glycosphingolipids throughout diverse cells, including endothelial cells, pericytes, vascular smooth muscle cells, renal epithelial cells, myocardial cells, neuronal cells, and the cornea. A primary source of Gb3 is postulated to be the membranes of senescent erythrocytes, which contain the glycosphingolipid precursor globose. Patients with FD and AB or B blood type also accumulate blood group B glycosphingolipids (those with α-galactosyl-terminated residues) and may have a more
aggressive disease (owing to a greater body substrate burden) than patients with blood group A or O.7,22 Particularly, Gb3 deposits in lysosomes of endothelial, perithelial, and smooth muscle cells of blood vessels determine vessel bulge into the lumen, which causes vessel narrowing and dilatation that progress to ischemia and infarction.22 This pathophysiologic mechanism explains the multisystemic nature of the condition.

The cardinal feature of classic FD (beginning in early childhood) is constant paresthesia (chronic burning, tingling, or nagging pain) usually affecting the hands and feet and persisting through adulthood.22,23 Acroparesthesia is the earliest major cause of morbidity during the first 2 decades of life and often remains undiagnosed unless other manifestations or a positive family history provide diagnostic clues.7 It can be interrupted by episodic Fabry crisis of incapacitating sharp pain lasting minutes to days, which can disappear with adulthood.23 Crises are often precipitated by stress, illness, temperature changes, or exercise and can be accompanied by fatigue, low-grade fever, and joint pain.23 Other neurologic findings may include auditory, vestibular, and sensory abnormalities.18,23 In the present series, all hemizygotes presented with acroparesthesia early in life (average age, 6 years), while only 2 of 5 heterozygotes reported this symptom.

The most obvious clinical feature is mucocutaneous lesions, also known as widespread AKs. They are defined as vascular lesions because they comprise one or more dilated blood vessels in the upper part of the dermis, directly subepidermal, accompanied in most cases by an epidermal reaction such as acanthosis and/or hyperkeratosis.8 Clinically, they present as innumerable small red to black papules, mostly with verrucous surfaces, which occur in clusters and are situated symmetrically in the bathing trunk area (buttocks, groin, umbilicus, and upper thighs). Isolated lesions begin with a minute reddish papule that enlarges up to 10 mm in diameter, becoming dark red to black with a discrete verrucous overgrowth.26,27

Angiokeratomas often do not appear until adolescence or young adulthood. The number of lesions and the extension over the body increase progressively with time so that generalization and mucosal involvement are frequent.8 The primary cause of the development of AKs in FD is the lysosomal storage of Gb3 in cutaneous endothelial cells with consequent weakness of the capillary wall and secondary ectasia.28 Isolated AKs are often mistaken for verruca vulgaris, hemangiomas, thrombosed capillary aneurysms, Spitz nevi, eruptive angiomomas, pyogenic granulomas, and other cutaneous entities. We also must differentiate them from other types of AKs such as solitary AKs, Fordyce AKs, AKs circumscriptum naeviforme, and AKs of Mibelli.6 The presence of AKs corporis diffusum is not pathognomonic of FD; these lesions may appear also in other lysosomal storage diseases.8,26,20,31 Furthermore, an idiopathic or cutaneous variant of AK corporis diffusum has been described as a specific clinical entity limited to the skin in patients without any metabolic disease.34,35 Nevertheless, the recently described cardiac and renal variants of FD frequently do not present with AKs.8,19 It could be that patients with these variants have specific mutations that determine markedly reduced enzyme transcript levels but result in sufficient residual α-gal A activity to modify the phenotype.8,19 Angiokeratomas can be symptomatically treated with different procedures such as excision surgery, electrocoagulation, liquid nitrogen, or laser.36 Sometimes AKs may become thrombosed and disappear without therapeutic intervention.37,38

In our series, 83% of hemizygotes had widespread AKs, and 80% of heterozygotes had isolated AKs. The presence or extent of cutaneous involvement does not correlate with systemic morbidity.

Hyphidrosis or anhidrosis usually presents in childhood or adolescence and is thought to be due to selective peripheral nerve damage,29 lipid deposits in the small blood vessels surrounding sweat glands,40 or lipid accumulation in the eccrine cells.23 It leads to dry skin and intolerance to heat and exercise. Interestingly, hyperhidrosis has also been reported in some patients.36 Decreased sweat production was a universal finding in our hemizygous population (6/6), but it was not present in the heterozygous group. Almost 50% of known patients also have reduced production of tears and saliva.23,41 When other causes are excluded, salivary dysfunction may be due to autonomic dysfunction or lipid deposition within the glands.42 Alterations in body hair density have also been described by some authors.36

Vascular alterations of the eyes are frequent findings27: conjunctival and retinal vessels (especially veins) are dilated and tortuous.7,13,43,44 Tortuosity of retinal vessels was the main characteristic in our hemizygous population. The corneal opacity associated with FD, visible only with slitlamp biomicroscopy, has a whorled pattern. It does not compromise vision and is a useful diagnostic indicator of FD. Less frequently, patients with FD have anterior capsular deposits in the lens or granular spokelike deposits on the posterior lens (Fabry cataract).43 In the present study, corneal opacities were present in 3 of 6 hemizygous men and in 2 of 5 obligate carriers. We detected cornea verticillata in 2 of 5 female patients. One hemizygous man had Fabry cataracts. None of the patients presented with visual impairment. There was no relation between ophthalmologic findings and systemic involvement.

Polyuria due to concentration defects may be the earliest renal symptom, but it is often ignored.7 Most patients with classic FD develop proteinuria in late adolescence, which is the first evidence of renal function impairment and tends to worsen with time.7 Polarization microscopy of the urinary sediment reveals birefringent lipid globules (renal tubular epithelial cells or cell fragments with lipid inclusions) with characteristic “Maltese cross” configuration.7,22 Renal failure usually occurs by the third to fifth decade of life, generally heralds the end stage of the disease, and is the most frequent cause of death among these patients.55 In the present series, only the older hemizygous man (age, 32 years) had renal impairment. Isolated proteinuria was detected at age 12 years and had been attributed at that time to a viral infection.

Cardiologic involvement frequently occurs in FD and is due to structural and functional changes related to glycosphingolipid deposition in the myocardium, valves, and conduction system.21 Common manifesta-
tions include left ventricular hypertrophy, mitral valve insufficiency, coronary artery disease, and conduction abnormalities. In our series, we found a high proportion of cardiac compromise in both groups with an early though asymptomatic presentation within the male population.

Patients with FD are vulnerable to early ischemic stroke of multifactorial origin. The risk of hemorrhagic stroke is also increased because of hypertension due to renal failure. The presence of cerebrovascular disease indicates a poor prognosis for both hemizygotes and heterozygotes. None of our patients had central nervous system involvement according to physical examination, electroneurography, and brain magnetic resonance imaging.

Although rare, FD remains an important diagnosis to consider in patients with AKs, with or without familial history. As dermatologists, we must have a high index of suspicion, especially when AKs are associated with other early symptoms of FD (mainly acroparesthesia, hypohidrosis, or heat intolerance). Once the diagnosis is established, prompt screening of family members, who may be affected or could be carriers, should be performed. In all cases, a multidisciplinary team is necessary for long-term follow-up and treatment.

Early detection of FD is now more important than ever. When used early, recombinant human α-gal replacement therapy gives patients a greater chance to reverse some of the cardiovascular and renal manifestations that occur in older individuals.

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REFERENCES

21. Kampmann C, Baehner F, Ries M, Beck M. Cardiac involvement in Anderson-
25. Morgan SH, Rudig P, Smith SJ, et al. The neurological complications of Anderson-
27. Caputo R, Ackerman BA, Sison-Torre RD. Fabry’s disease (Angiokeratoma cor-
33. Kawanishi Y, Matsu-ura K, Sakuraba H, Otsuka F. Angiokeratoma corporis diffu-
34. Laxminas H, Thappa DM, Karthikeyan K. Cutaneous variant of angiokeratoma cor-
poris diffusum. Dermatol Online J. 2003:1;133.

Announcement

New Address for Editorial Office

The ARCHIVES editorial office has moved. Effective October 1, 2004, editorial correspondence and manuscripts should be sent to the new address: June K. Robinson, MD, Editor, Archives of Dermatology, Section of Dermatology, Level 2, Bldg 11, Room 503, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756-0001; telephone: (603) 653-9477; fax: (603) 653-9478. Short manuscripts without figures or tables and letters to the editor may continue to be sent electronically to archdermatol@jama-archives.org.