Anderson-Fabry Disease: Enzyme Replacement Therapy

Alvaro Leon-Mateos[1], Virginia Fernández-Redondo[1], Andrés Beiras[2] and Jaime Toribio[1]

Departments of [1]Dermatology and [2]Pathology, Clinical University Hospital, Faculty of Medicine, C/San Francisco s/n, 15782 Santiago de Compostela, Spain. E-mail: mejaime@usc.es
Accepted July 24, 2003

Sir,

Anderson-Fabry disease is a metabolic lysosomal storage disease caused by a deficiency of the enzyme α-galactosidase A and inherited as an X-linked recessive trait. The progressive accumulation of glycosphingolipids (globotriaosylceramide, GB3) in blood, vessels and cells from several organs and tissues causes significant multi-systemic damage in homozygous males and in carrier females.

For decades there has been no specific aetiological treatment for this disease, but recently a new enzyme replacement therapy has been developed by genetic engineering techniques.

We present here a case of Fabry disease diagnosed in our department. The patient is currently on a course of enzyme replacement treatment with agalsidase alpha.

CASE REPORT

A 20-year-old male was referred to us because of punctiform cutaneous lesions on the palms. He had been suffering for 4 years from recurrent attacks in the arms and legs associated with fever, and precipitated by a hot environment and intense physical exercise. He presented no other relevant medical record. Some male relatives had died suddenly in early adulthood, but no history of cutaneous disease was known in the family (Fig. 1).

Dermatological examination showed small, purple-red, punctiform lesions, slightly palpable and grouped together on the hands, feet, scrotum, buttocks and proximal area of the lower extremities, suggestive of angiokeratomas (Fig. 2).

The histopathology of one of these lesions showed dilatation of the vasculature in the papillary dermis and hyperkeratosis in the supra-adjacent epidermis. The ultrastructural analysis revealed the presence of electron-dense lamellar cytoplasmic inclusions of 4 nm of periodicity in the vascular endothelium (Fig. 3).

Complementary studies (blood analysis, hepatic enzymes, renal function, electrocardiogram, echocardiogram and chest X-rays) were normal. Ophthalmologic examination showed corneal opacity and vascular tortuosity of the retina.

The α-galactosidase A level in leucocytes was 8.7 nmol min^{-1} g^{-1} (control: 1123). Subsequent molecular study of the enzyme gene demonstrated the 1033delTC mutation (1). The same mutation was detected in the patient's mother, while another 16 relatives presented a normal molecular analysis. No angiokeratomas were observed in any of the 30 relatives examined.

DISCUSSION

A recent study by Meikle et al. (2) sets the prevalence of Anderson-Fabry disease at 1 in 117,000 newborn children. This is probably an underestimate, with the real number likely to be around 1:40,000 (3). A congenital decrease of the α-galactosidase A levels produces a systemic accumulation of GB3 causing the appearance of multisystem manifestations (Table I). More than 150 different mutations have been identified,

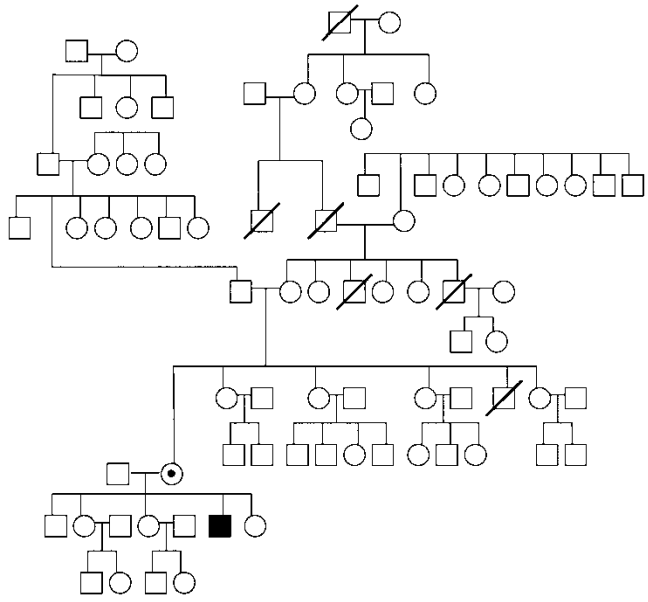

Fig. 1. Patient's pedigree. Index case (■), carrier (⦿) and several dead young males (⍁) were detected.

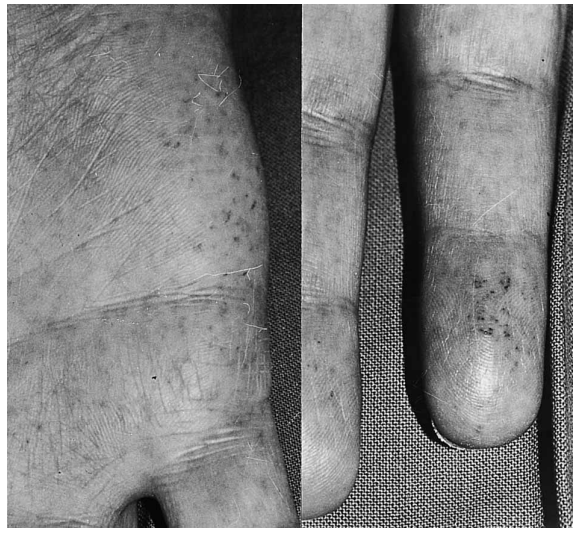

Fig. 2. Multiple small angiokeratomas distributed in groups on the hands.

DOI: 10.1080/00015550310020602

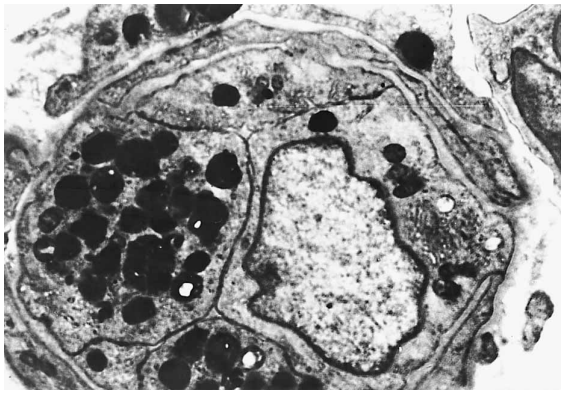

Fig. 3. Ultrastructural analysis from a biopsy of the skin showed endothelial cells containing intracytoplasmatic osmiophilic bodies with characteristic "zebra" or "onion-skin" appearance due to concentric lamellation of alternating clear and dark layers (×4,200).

among these the 1033delTC deletion found in our patient (1).

Male patients usually present in adolescence with paroxysmal fever, hypohidrosis, acroparaesthesias, cornea verticillata and angiokeratoma corporis diffusum (ACD). If left untreated, cardiac alterations, cerebrovascular accidents and progressive renal failure usually lead to death during the fourth or fifth decade. Heterozygous females seem to present a milder and more late-developing form of the disease, with a decrease in the average life expectancy of about 15 years compared to the general population (4).

The presence of angiokeratomas is one of the earliest and most frequent manifestations of Anderson-Fabry disease; it is present in 71% of male patients (5) and in 35% of heterozygous carrier females (4). The average age of presentation in males is 16.8 years, but the diagnosis is often delayed by 10 or more years (4). ACD was classically considered to be synonymous with Anderson-Fabry disease, but is known today to be present in other lysosomal storage diseases too (6, 7).

Table I. *Clinical manifestations of Anderson-Fabry disease*

Cutaneous: Angiokeratoma corporis diffusum
Ocular: Cornea verticillata
Vascular, retinal and conjunctival alterations
Lenticular opacities
Cardiovascular: Hypertension
Left ventricular hypertrophy
Valvular disease
Arrhythmia
Angina and myocardial infarction
Renal: Proteinuria, haematuria
Proximal and distal tubular disease
Renal failure
Neurological: Hypohidrosis
Acroparesthesias, pain crisis
Cerebrovascular accidents
Gastrointestinal: Nausea, vomiting
Abdominal pain, diarrhoea
Psychiatric: Depression, suicidal tendency

Although cosmetic treatment of angiokeratomas of Fabry disease has been based on the use of laser systems (8), only recently has aetiological therapy become available. The new enzyme replacement treatment with α-galactosidase A seems to reduce GB3 levels in blood and urine, leading to improved cardiac and renal functioning as well as control of the pain crisis (9, 10). Our patient has been treated during the past 6 months with agalsidase alpha (Replagal) every 14 days in a dose of 0.2 mg kg^{-1} i.v. administered over a 40-min period. A marked decrease of the pain in the arms and legs has been reported by the patient, and there have been no important infusion-associated reactions or other side effects.

ACKNOWLEDGEMENTS

We thank Dr. A. Chabás of the Clinical Biochemistry Institute in Barcelona for her support in the enzymatic and molecular studies of this family.

REFERENCES

1. Ashley GA, Shabbeer J, Yasuda M, Eng CM, Desnick RJ. Fabry disease: twenty novel alpha-galactosidase A mutations causing the classical phenotype. J Hum Genet 2001; 46: 192–196.
2. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999; 281: 249–254.
3. Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic bases of inherited disease, 8th ed. New York: McGraw-Hill, 2001: 3733–3774.
4. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet 2001; 38: 769–775.
5. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet 2001; 38: 750–760.
6. Venencie PY, Pauwels C, Malherbe V, Perie G, Landrieu P. Angiokeratomes et fucosidose. Etude immunohistochimique et ultrastructurale. Ann Dermatol Venereol 1995; 122: 432–435.
7. Vargas-Díez E, Chabás A, Coll MJ, Sánchez-Pérez J, García-Díez A, Fernández-Herrera JM. Angiokeratoma corporis diffusum in a Spanish patient with aspartylglucosaminuria. Br J Dermatol 2002; 147: 760–764.
8. Mohrenschlager M, Braun-Falco M, Ring J, Abeck D. Fabry disease: recognition and management of cutaneous manifestations. Am J Clin Dermatol 2003; 4: 189–196.
9. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. N Engl J Med 2001; 345: 9–16.
10. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001; 285: 2743–2749.