Fabry disease. A case report

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SUMMARY

Fabry disease is an under-recognized X-linked recessive lysosomal storage disorder resulting from the deficient activity of the enzyme α-galactosidase A (α-Gal A). The first case of Fabry disease in Slovenia was diagnosed in 1991. This 46 year-old male was referred for dermatologic evaluation of a purpura on his abdomen. He was being treated for proteinuria and cardiac symptoms. The diagnosis of *angiokeratoma corporis diffusm* (Fabry disease) was made clinically and confirmed by demonstration of deficient leukocyte α-Gal A activity. The patient subsequently developed cerebrovascular symptoms, coronary disease, and renal failure, and died from a recurrent myocardial infarction. Family studies identified several other affected males and carrier female relatives with this X-linked recessive disorder. This case illustrates the typical multi-manifestations of this inherited disease which now can be safely and effectively treated by enzyme replacement therapy. Early diagnosis is important for the most effective treatment of this disease.

KEY WORDS

Fabry disease, angiokeratoma corporis diffusum, X-linked recessive inheritance, α-galactosidase A activity, enzyme replacement therapy

Introduction

The German dermatologist, Johannes Fabry and the English dermatologist, William Anderson, independently described the first patients with Fabry disease in 1898 (1, 2). Fabry disease is an X-linked recessive inborn error of glycosphingolipid catabolism resulting from the deficient or absent activity of the lysosomal enzyme, α-galactosidase A (α-Gal A) (3, 4). The enzymatic defect leads to the systemic accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids in the plasma and in tissue lysosomes (4). Males are primarily affected, while females are carriers who may have clinical manifestations.

In classically affected males, the symptoms usually become manifest in childhood, with patients typically presenting with acroparesthesias, burning tingling pains in the upper and lower extremities. They also experience episodic attacks of excruciating pain, known as Fabry crises, which are triggered by fevers, exercise, stress and/or dramatic changes in the weather. Decreased sweating (hypohidrosis) or even anhydrosis is also present as are the typical skin lesions (angiokeratomas) typically present

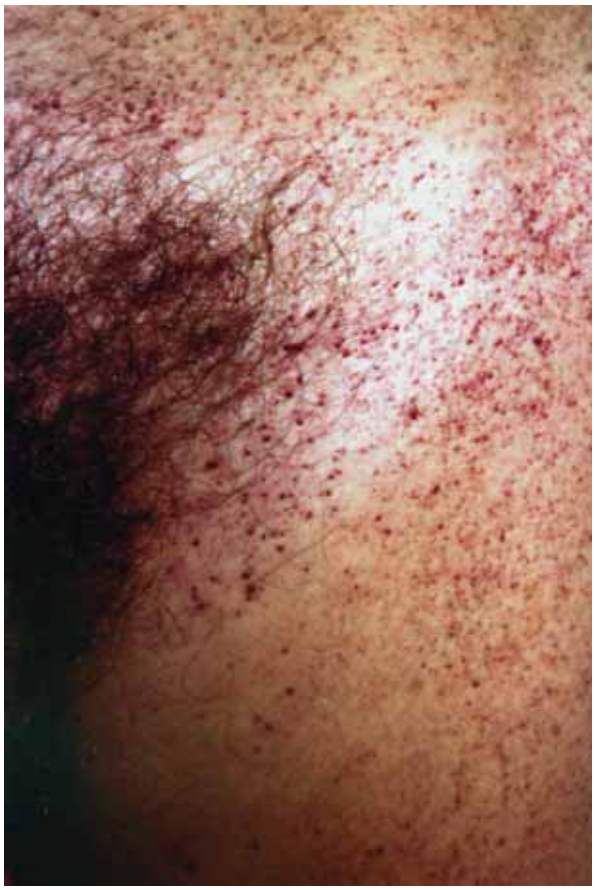

Figure 1. Numerous angiokeratomas in the inguinal region and on the lower abdomen.

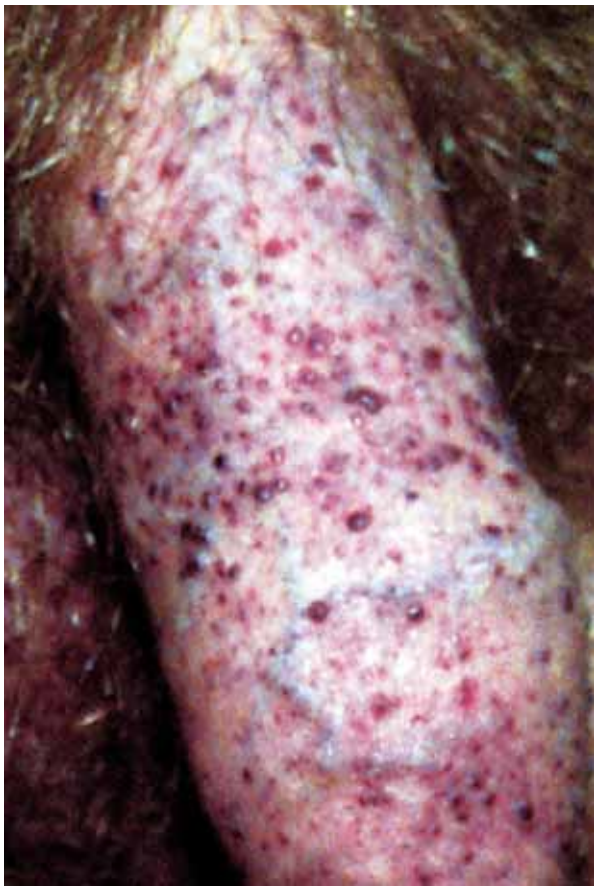

Figure 2. Angiomas and angiokeratomas in the genital area.

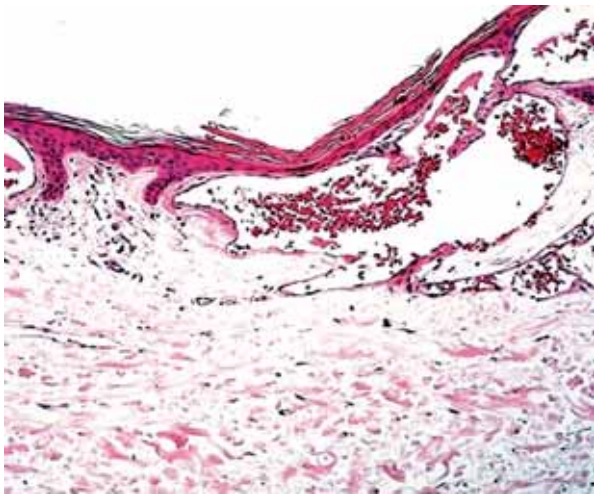

Figure 3. Angiokeratoma Fabry, histopathology (HE stain, magnification x 200): two angiomas located subepidermally. The epidermis is thin and flattened. The corneal layer is moderately thickened with elements of parakeratosis. Large vascular spaces containing erithrocytes.

on the abdomen, buttocks, flanks, penis, and scrotum. Young patients also have corneal opacities, postprandial abdominal cramping, diarrhea, left ventricular hypertrophy and proteinuria (4). With advancing age, the progressive lysosomal GL-3 accumulation, particularly in the vascular endothelium, leads to renal failure, vascular disease of the heart and the brain, and premature demise in the fourth and fifth decades of life (4-6). In the absence of a previously diagnosed family member, the disease is often recognized only after patients experience the severe late complications of the disease including cardiac and renal failure.

Recently, later-onset cardiac and renal variants which have residual α-Gal A activity have been described. These variants lack the manifestations which are the hallmarks of the classic phenotype, including the angiokeratomas, acroparesthesias, hypohidrosis, and ocular abnormalities. The variants typically present in the sixth decade of life or later with renal and/or cardiac disease (7-10).

Affected males with the classic or variant phenotypes can be reliably diagnosed by the demonstration of markedly deficient α-Gal A activity in plasma, isolated leukocytes, and/or cultured cells (11). Classically affected males

have essentially no α-Gal A activity, while the cardiac and renal variants have residual activity due to missense mutations in the α-Gal A gene. Identification of the specific mutation in the patient's α-Gal A gene confirms the diagnosis. To date, over 400 different α-Gal A mutations causing Fabry disease have been identified. Most are family-specific as no common mutations (present in >5% of patients) have been detected (12). Carrier females for either the classic or variant phenotypes have markedly variable α-Gal A activities because of random X-chromosomal inactivation (4) and, therefore, measurement of plasma and/or leukocyte α-Gal A activity may be misleading. Accurate diagnosis of heterozygous females requires demonstration of the specific family mutation in the α-Gal A gene (13).

Case report

In May of 1991, a 46-year-old male was admitted to the Department of Internal Medicine, Slovenj Gradec General Hospital for evaluation of proteinuria, non-specific cardiac symptoms, and a possible vasculopathy. He had reddish macular-papular skin lesions since the age of 13 years. As a youth, he experienced acroparesthesias, joint pains, and did not perspire in hot weather. There was no known family history of skin lesions.

The patient was referred for a dermatologic examination. He had diffuse red to blue papules in the gluteal, lower abdominal and inguinal regions (Figure 1), and on the scrotum and penis (Figure 2). In between the papules were reddish macular lesions. He had similar lesions around the navel and the nipples; less numerous lesions were also present in the armpits and on the flexor aspects of the thighs. Lesions were also seen on his buccal mucosa, upper lip, and his palms and soles. The history, clinical symptoms and the evolution of the disorder were consistent with the diagnosis of *angiokeratoma corporis diffusum* (Fabry disease).

Routine hematological tests were normal including the coagulation profile. Renal function was normal except for mild proteinuria, up to 0.46 g/L. Electrocardiography disclosed a sinusoidal rhythm and concentric hypertrophy of the left ventricle. Echography also showed concentric hypertrophy of the left ventricle and normal systolic activity; the intraventricular septum was thickened and had an unusual granular structure. Ophthalmologic investigation revealed aneurysmal dilatations of the conjunctival vessels, and diffuse corneal opacities (i.e., corneal verticillata).

Histologic examination of a skin biopsy from the left side of the abdomen revealed a moderate hyperkeratosis (Figure 3). In the upper dermis, there were enormously dilated vessels filled with erythrocytes. Some vessels were surrounded by epithelial sprouts. In the dermis, a moderate lymphohistiocytic infiltrate was observed. Histologic examination of the rectal mucosa disclosed no signs of amyloidosis. These findings were consistent with the diagnosis of angiokeratoma corporis diffusum (Fabry disease).

Biochemical confirmation of the clinical and histologic diagnoses of Fabry disease was made by determining the leukocyte α-Gal A activity, which was totally deficient. The enzyme assay was performed at the Institute for Biochemistry of the Medical Faculty in Zagreb. Subsequently, the patient's α-Gal A mutation was identified as a missense mutation, N272S, the substitution of a serine for an asparagine residue at amino acid 272 in the α-Gal A polypeptide (14). Family studies by mutation analysis diagnosed six other affected males from 28 to 57 years old and 10 female carriers (14).

The patient began to experience serious complications of the disease in 1992, when an ischemic cerebrovascular event occurred with a right-sided palsy, from which the patient satisfactorily recovered. In 1997, he suffered a recurrent stroke, causing a left-side palsy. His creatinine had increased to 170 mmol/L. In January 2000, his progressive renal insufficiency required chronic hemodialysis. During a hospitalization for hemodialysis, he had a heart attack, after which paroxysmal atrial fibrillation developed and he was treated with warfarin (Marivarin^{R}, Krka). He subsequently suffered from acute cholelithiasis and an endoscopic cholecystectomy was performed. During the following two years, he had three bouts of bronchopneumonia. In January 2003, an acute myocardial infarction occurred from which he expired at the age of 58 years.

Discussion

Fabry disease is a rare inborn error of glycosphingolipid catabolism. The incidence of the classic phenotype is about 1:40,000 to 1:60,000 males (4, 15), suggesting that in Slovenia there are at least 50 classically affected males with Fabry disease. The patient reported here was the first case diagnosed in Slovenia. Subsequent family studies revealed that his mother was a carrier of this X-linked recessive disorder, and the disease was diagnosed in four of his brothers and two of his nephews. In addition, two sisters were identified as carriers and all the daughters of the affected males were obligate carriers of the Fabry gene (14).

Early diagnosis of Fabry disease is important. Because of the typical skin lesions, dermatologists are often the first to make the diagnosis. Prior to 2001, treatment of the disease was limited to palliative and non-specific treatment of the renal, cardiac, and cerebrovascular complications. However, enzyme replacement therapy (ERT) for Fabry disease was introduced in Europe in 2001. ERT has been shown to clear the accumulated GL-3 in the blood vessels as well as in the cells of the heart, kidney, and skin (16-21). Clinically, ERT has resulted in stabilized renal function, decreased abdominal cramping, decreased cardiac mass, and markedly improved quality of life (22-26).

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REFERENCES

1. Anderson W. A case of angiokeratoma. Br J Dermatol 1898; 10: 113.

2. Fabry J. Ein Beitrag Zur Kenntnis der Purpura haemorrhagica nodularis (Purpura papulosa hemorrhagica Habrae). Arch Dermatol Syph 1898; 43: 187.

3. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med 1967; 276: 1163-7.

4. Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase A deficiency: Fabry disease In: Scriver CR, Beaudet AL, Sly WS et al, (eds): *The Metabolic and Molecular Bases of Inherited Disease*. McGraw-Hill, 2001, p 3733-74.

5. Colombi A, Kostyal A, Bracher R, Gloor F, Mazzi R, Tholen H. Angiokeratoma corporis diffusum - Fabry's disease. Helv Med Acta 1967; 34: 67-83.

6. 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: 750-60.

7. Elleder M, Bradova V, Smid F, Budesinsky M, Harzer K, Kustermann-Kuhn B, Ledvinova J, Belohlavek, Kral V, Dorazilova V. Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease. Report on a case simulating hypertrophic non-obstructive cardiomyopathy. Virchows Arch A Pathol Anat Histopathol 1990; 417: 449-55.

8. von Scheidt W, Eng CM, Fitzmaurice TF, Erdmann E, Hubner G, Olsen EG, Christomanou H, Kandolf R, Bishop DF, Desnick RJ. An atypical variant of Fabry's disease with manifestations confined to the myocardium. N Engl J Med 1991; 324: 395-9.

9. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, Yoshida A, Kuriyama M, Hayashibe H, Sakuraba H, Tanaka H. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med 1995; 333: 288-93.

10. Nakao S, Kodama C, Takenaka T, Tanaka A, Yasumoto Y, Yoshida A, Kanzaki T, Enriquez ALD, Eng CE, Tanaka H, Tei C, Desnick RJ. Fabry disease: Detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. Kidney Int 2003; 64: 801-7.

11. Desnick RJ, Allen KY, Desnick SJ, Raman MK, Bernlohr RW, Krivit W. Fabry's disease: Enzymatic diagnosis of hemizygotes and heterozygotes. α-Galactosidase activities in plasma, serum, urine, and leukocytes. J Lab Clin Med 1973; 81: 157-71.

12. Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, Thomas NS, Abeysinghe S, Krawczak M, Cooper DN. Human Gene Mutation Database (HGMD): 2003 update. Hum Mutat 2003; 21: 577-81.

13. Ashton-Prolla P, Ashley GA, Giuglianai R, Pires RF, Desnick RJ, Eng CM. Fabry disease: Comparison of enzyzmatic, linkage and mutation analysis in a family with a novel mutation (30 del G). Am J Med Genet 1999; 84: 420-4.

14. Verovnik F, Benko D, Vujkovac B, Linthorst GE. Remarkable variability in renal disease in a large Slovenian family with Fabry disease. Eur J Hum Genet 2004; 12: 678-81.

15. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999; 281: 249-54.

16. Eng CM, Banikazemi M, Gordon R, Goldman M, Phelps R, Kim L, Gass A, Winston J, Dickman S, Stacy CB, Fallon JT, Brodie S, Mehta D, Parsons R, Norton K, O'Callaghan M, Desnick RJ. A phase 1/2 clinical trial of enzyme replacement in Fabry disease: Pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet 2001; 68: 711-22.

17. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ.

Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. N Eng J Med 2001; 345: 9-16.

18. Schiffmann R, Kopp JB, Austin HA, 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001; 285: 2743-9.

19. Thurberg BL, Rennke H, Colvin RB, Dikman S, Gordon RE, Collins AB, Desnick RJ, O'Callaghan M. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int 2002; 62: 1933-46.

20. Wilcox WR, Banikazemi M, Guffon N, Waldek S, Lee P, Linthorst GE, Desnick RJ, Germain DP. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet 2004; 75: 65-74.

21. Thurberg BL, Randolph Byers H, Granter SR, Phelps RG, Gordon RE, O'Callaghan M. Monitoring the 3-year efficacy of enzyme replacement therapy in Fabry disease by repeated skin biopsies. J Invest Dermatol 2004; 122: 900-8.

22. De Schoenmakere G, Chauveau D, Grunfeld JP. Enzyme replacement therapy in Anderson-Fabry's disease: beneficial clinical effect on vital organ function. Nephrol Dial Transplant 2003; 18: 33-5.

23. Waldek S. PR interval and the response to enzyme-replacement therapy for Fabry's disease. N Engl J Med 2003; 348: 1186-7.

24. Weidemann F, Breunig F, Beer M, Sandstede J, Turschner O, Voelker W, Ertl G, Knoll A, Wanner C, Strotmann JM. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. Circulation 2003; 108: 1299-301.

25. Hilz MJ, Brys M, Marthol H, Stemper B, Dutsch M. Enzyme replacement therapy improves function of C-, Aδ-, and Aβ-nerve fibers in Fabry neuropathy. Neurology 2004; 62: 1066-72.

26. Guffon N, Fouilhoux A. Clinical benefit in Fabry patients given enzyme replacement therapy: a case series. J Inherit Metab Dis 2004; 27: 221-7.

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