FABRY DISEASE: DIAGNOSIS OF A RARE DISORDER

DOENÇA DE FABRY: DIAGNÓSTICO DE UMA DOENÇA RARA

Cristina Netto[1], Maira Burin[1], Laura Jardim[1,5], Marilyn Tsao[1], Fernanda Pereira[3], Ursula Matte[3], Roberto Giugliani[1,4], Elvino Barros[2,5], Daiana Porsch[2], Vagner Milani[2], Liana Rossato[2], Ane Nunes[2]

ABSTRACT

Fabry disease (FD) is an X-linked inborn error of glycosphingolipid metabolism due to the deficiency of α-galactosidase A. The progressive accumulation of globotriaosylceramide (Gb3), particularly in the vascular endothelium, leads to renal, cardiac, and cerebrovascular manifestations and early death. Clinical manifestations include the onset of pain and paresthesias in extremities, angiokeratoma and hypohidrosis during childhood or adolescence. Proteinuria and lymphedema occur with increasing age. Severe renal impairment leads to hypertension and uremia. Death usually occurs due to renal failure or cardiac or cerebrovascular disease. Disease presentation may be subtle, and its signs and symptoms are often discounted as malingering or are mistakenly attributed to other disorders, such as rheumatic fever, neurosis, multiple sclerosis, lupus, or petechiae.

We present a 46-year-old man who since adolescence has suffered from painful acroparesthesia, disseminated skin angiokeratomas, hypohidrosis and heat intolerance. He was submitted to a thorough investigation with different specialists, but never reached a diagnosis. He started hemodialysis 3 years ago and at the moment is in standby for kidney transplantation. He was enrolled in a Brazilian FD screening and a reduced serum activity of α-galactosidase A (0.0027 nmol/h/mL – reference value 4-22) confirmed the diagnosis of FD.

He has angiokeratoma at the bottom area, his echocardiogram demonstrated left ventricular hypertrophy and the family history is very rich, as the patient has 15 siblings.

This case represents a very common story for FD patients. They usually spend most of their lives trying to find someone who could understand or explain their suffering. These results indicate that FD may be much more common among male dialysis patients than previously recognized. Subsequently, FD should be considered in every patient with unexplained renal disease, especially when cardiac or cerebral complications suggest an underlying multisystemic disorder. Early diagnosis of FD is important because it allows family studies to identify other affected relatives for genetic counseling and therapeutic intervention.

Keywords: Chronic kidney disease, enzyme replacement therapy, Fabry disease, angiokeratoma corporis diffusum, α-galactosidase, agalsidase, lysosomal diseases, renal dysfunction.

RESUMO

A doença de Fabry (DF) é um erro inato do metabolismo dos glicoesfingolipídeos devido à deficiência da α-galactosidase A. O acúmulo progressivo de globotriaosilceramida (Gb3),

[1] Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS.
[2] Serviço de Nefrologia, HCPA, Porto Alegre, RS.
[3] Centro de Terapia Gênica, HCPA, Porto Alegre, RS.
[4] Departamento de Genética, Instituto de Biociências, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS.
[5] Departamento de Medicina Interna, Faculdade de Medicina, UFRGS, Porto Alegre, RS.
Correspondence: Cristina Netto, Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, CEP 90035-903, Porto Alegre, RS. Tel.: (51) 2101.8011. E-mail: Cristina.Netto@ufrgs.br.

particularmente no endotélio vascular, leva a manifestações renais, cardíacas e cerebrovasculares e morte precoce. As manifestações clínicas incluem o início, durante a infância ou adolescência, de episódios de dor e parestesias nas extremidades, angioqueratomas e hipohidrose. Com a idade, podem aparecer proteinúria e linfedema. Insuficiência renal grave leva à hipertensão e uremia. O óbito ocorre devido à insuficiência renal ou doença cardíaca ou cerebrovascular. A apresentação da doença pode ser sutil, e seus sinais e sintomas são erroneamente atribuídos a outras doenças, como febre reumática, neurose, esclerose múltipla, lúpus ou petéquias.

Relatamos o caso de um paciente masculino com 46 anos que, desde a adolescência, sofre de acroparestesia, angioqueratomas disseminados, hipohidrose e intolerância ao calor. Ele foi submetido a extensa investigação com diferentes especialistas, mas nunca chegou a um diagnóstico. Iniciou hemodiálise há 3 anos e, no momento, está na lista de espera para transplante de rim. Participou de um programa brasileiro de triagem para DF, e uma atividade reduzida de α-galactosidase A (0,0027 nmol/h/mL – valor de referência 4-22) confirmou o diagnóstico de DF.

O paciente apresenta angioqueratomas na área do calção, seu ecocardiograma demonstra hipertrofia ventricular esquerda e sua história familiar é rica, pois ele tem 15 irmãos.

Este caso representa uma história muito comum entre pacientes com DF. Eles geralmente passam a maior parte de suas vidas tentando encontrar alguém que compreenda ou explique seu sofrimento. Estes resultados indicam que a DF pode ser muito mais comum entre homens que realizam hemodiálise do que antes previsto. Subseqüentemente, a DF deve ser considerada em todo paciente com doença renal sem causa aparente, principalmente quando complicações cardíacas ou cerebrovasculares sugerirem uma doença multissistêmica. O diagnóstico precoce da DF é importante, pois permite estudo familiar para identificar parentes afetados para aconselhamento genético e intervenção terapêutica.

Unitermos: Doença renal crônica, terapia de reposição enzimática, doença de Fabry, angioqueratoma *corporis diffusum*, α-galactosidase, agalsidase, doenças lisossômicas, disfunção renal.

INTRODUCTION

Fabry disease (FD) is an X-linked inborn error of glycosphingolipid metabolism due to the deficiency of α-galactosidase A. Reduced activity of α-galactosidase A causes storage of globotriaosylceramide (Gb3) inside cell lysosomes. Its progressive accumulation, particularly in the vascular endothelium, leads to renal, cardiac, and cerebrovascular manifestations and early death. The disease is panethnic, and incidence estimates range from about 1 in 40,000 to 60,000 males (1).

Clinical manifestations in classically affected hemizygotes who have no detectable α-galactosidase A activity include the onset of pain and paresthesias in extremities, vessel ectasia (angiokeratoma) in skin and mucous membranes, and hypohidrosis during childhood or adolescence. Corneal and lenticular opacities are also early findings. Proteinuria and lymphedema occur with increasing age. Severe renal impairment leads to hypertension and uremia. Death usually occurs due to renal failure or cardiac or cerebrovascular disease. Some of these manifestations have been already studied by us (2-4).

Although clinical onset occurs in childhood, disease presentation may be subtle, and its signs and symptoms are often discounted as malingering or are mistakenly attributed to other disorders, such as rheumatic fever, neurosis, multiple sclerosis, lupus, or petechiae.

FD predominantly affects males, but in contrast to some other diseases with X-linked inheritance, most female heterozygotes are also affected but do not always present with the classic phenotype.

CASE REPORT

We present a 46-year-old man who since adolescence has suffered from painful acroparesthesia, disseminated skin angiokeratomas, hypohidrosis and heat intolerance.

During his life, he has been submitted to a thorough investigation with different specialists, but never reached a diagnosis. Three years ago he was diagnosed with renal insufficiency, progressing to end-stage renal disease 1 year ago when he started

hemodialysis. At the moment, he is in standby for kidney transplantation. He also has left ventricular hypertrophy and impaired vision.

This patient was enrolled in a Brazilian FD screening and a reduced serum activity of α-galactosidase A (0.0027 nmol/h/mL – reference value 4-22) confirmed the diagnosis of FD.

On physical examination the patient was normotensive, and his body weight was 61.500 kg. Cutaneous lesions were located at the bottom area. These lesions were first noticed during adolescence, and progressively increased in number with time.

His echocardiogram demonstrated left ventricular hypertrophy, but his electrocardiogram (EKG) did not show conduction abnormalities. Serum creatinine was 6.8 mg/dL (normal range 0.6-1.3), urea 74 mg/dL (normal range 13-43). A biopsy of the kidney revealed tubular atrophy, interstitial fibrosis and glomerular sclerosis.

The family history is very rich, as the patient has 15 siblings. He has a brother who died of renal failure at 35. Genetic counseling was able to identify one nephew who also has reduced serum activity of α-galactosidase A (0.05 nmol/h/mL – reference value 4-22), with only mild symptoms of FD. Molecular analysis is under way to diagnosis the female relatives.

DISCUSSION

This case represents a very common story for Fabry patients. They usually spend most of their lives trying to find someone who could understand or explain their suffering.

Because FD is not common or well known and its early classical manifestations tend to be nonspecific, the disorder is often unrecognized, misdiagnosed, or diagnosed late in life. Males with classical phenotype typically present in childhood with the characteristic angiokeratoma and acroparesthesias. However, if these signs and symptoms are subtle or absent, the disorder may not be recognized until adulthood, when proteinuria, renal insufficiency, and/or cardiomyopathy are detected and the diagnosis is belatedly made (5).

Renal involvement has been recognized as a cardinal feature of FD, since patients with characteristic skin lesions and albuminuria were first described in 1898 (6).

The renal manifestation results from GL3 deposition in podocytes, mesangium, glomerular endothelium, epithelium of the loop of Henle and the distal tubule, arterial and arteriolar endothelial and smooth muscle cells, and interstitial cells (7). The deposition in the renal vascular endothelium is progressive and associated with interstitial fibrosis and glomerulosclerosis (8). End-stage renal disease usually occurs in the third to fifth decade of life (9).

Screening efforts can be carried out in subpopulations thought to be at higher risk for the disease than the general population. Dialysis screening efforts seem to be worthwhile, since kidney failure is an important outcome in FD. Nakao et al. (10) screened 514 consecutive males and found six who had low levels of serum α-galactosidase, for a prevalence of 1.2%. Large scale screening efforts of dialysis populations have been carried out in the Netherlands and Austria.

These results indicate that FD may be much more common among male dialysis patients than previously recognized. Apparently, FD is seldom recognized as a cause of renal failure and, as a consequence, is possibly underdiagnosed. Subsequently, FD should be considered in every patient with unexplained renal disease, especially when cardiac or cerebral complications suggest an underlying multisystemic disorder.

In males FD can reliably be diagnosed by α-galactosidase A activity determination. This could then be followed by screening of family members for FD, in whom progression of renal failure or other organ failure due to disease may be detected at an earlier stage, enabling appropriate intervention.

Early diagnosis of FD is important because it allows family studies to identify other affected relatives for genetic counseling and therapeutic intervention. This is especially true now that clinical studies have shown the safety and effectiveness of enzyme replacement therapy for FD (11,12), as well as the potential for enzyme enhancement therapy (13).

REFERENCES

1. Desnick R, Ioannou Y, Eng C. a-galactosidase a deficiency: Fabry disease. In: Scriver CR, Sly WS, Beaudet AL, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill. 2001. Pp. 3733-4.
2. Ashton-Prolla P, Ashley GA, Giugliani R, Pires RF, Desnick RJ, Eng CM. Fabry disease: comparison of enzymatic, linkage, and mutation analysis for carrier detection in a family with a novel mutation (30delG). Am J Med Genet. 1999;84(5):420-4.
3. Gomes I, Nora DB, Becker J, et al. Nerve conduction studies, electromyography and sympathetic skin response in Fabry's disease. J Neurol Sci. 2003;214(1-2):21-5.
4. Jardim L, Vedolin L, Schwartz IV, et al. CNS involvement in Fabry disease: clinical and imaging studies before and after 12 months of enzyme

replacement therapy. J Inherit Metab Dis. 2004;27(2):229-40.
5. Clarke JT, Knaack J, Crawhall JC, Wolfe LS. Ceramide trihexosidosis (Fabry's disease) without skin lesions. N Engl J Med. 1971;284(5):233-5.
6. Fabry H. An historical overview of Fabry disease. J Inherit Metab Dis. 2001;24 Suppl 2:3-7.
7. Meroni M, Sessa A, Battini G, Tazzari S, Torri Tarelli L. Kidney involvement in Anderson-Fabry disease. Contrib Nephrol. 1997;122:178-84.
8. Bernstein J, Churg J. Heritable metabolic diseases. In: Jenette JC, Olson JL, Schwarts MM, Silva FG, editors. Heptinstall's pathology of the kidney. Philadelphia: Lippincott-Raven; 1999. Pp. 1289-92.
9. Thadhani R, Wolf M, West ML, et al. Patients with Fabry disease on dialysis in the United States. Kidney Int. 2002;61(1):249-55.
10. Nakao S, Kodama C, Takenaka T, et al. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. Kid Int. 2003;64(3):801-7.
11. Schiffmann R, Murray GJ, Treco D, et al. Infusion of alpha-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. Proc Natl Acad Sci USA. 2000;97(1):365-70.
12. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A – replacement therapy in Fabry's disease. N Engl J Med. 2001;345(1):9-16.
13. Desnick RJ, Schuchman EH. Enzyme replacement and enhancement therapies: lessons from lysosomal disorders. Nat Rev Genet. 2002;3(12):954-66.