Rev Med Hosp Gen Méx. 2016;xxx(xx):xxx–xxx

REVISTA MÉDICA DEL
HOSPITAL GENERAL
DE MÉXICO
www.elsevier.es/hgmx

CLINICAL CASE

Histopathological findings in renal biopsies in Anderson–Fabry disease. Case series

A.L. Mena Rodríguez*, **M.V. Soto Abraham, M.Y. Valdespino Vázquez, B. de León Garza**

Pathology Department, Hospital General de México, Mexico City, Mexico

Received 8 March 2016; accepted 29 August 2016

KEYWORDS
Anderson–Fabry disease;
alpha-Galactosidase deficiency;
Lysosomal storage disease

Abstract Anderson–Fabry disease is the second most common lysosomal storage disease after Gaucher disease. It is an X-linked lysosomal disorder that causes a deficiency in alpha-galactosidase, leading to the accumulation of globotriaosylceramide (Gb3) in the lysosomes of different cells, producing renal, cardiac and neurological deficits that can lead to an early death. The renal histologic analysis, applied using a standardised rating system, is useful for initiating enzyme replacement therapy and for assessing the prognosis. In this article we classify the histologic lesions found in light and electron microscopy in renal biopsies of patients with Anderson–Fabry disease, using the scoring system for renal pathology in Fabry disease: Report of the International Study Group of Fabry Nephropathy (ISGFN). More than half of the cases did not present any change in the clinical and laboratory assessment at the time of the biopsy; nevertheless there were changes in the light and electronic microscopy findings. The information from the renal biopsy is an early indicator of renal damage, even without proteinuria and with preserved renal function.

PALABRAS CLAVE
Enfermedad de Fabry-Anderson;
Déficit de α-galactosidasa;
Enfermedad de depósito lisosomal

Hallazgos histopatológicos en biopsias renales en enfermedad de Fabry-Anderson. Serie de casos

Resumen La enfermedad de Fabry-Anderson es la segunda enfermedad de depósito lisosomal más frecuente después de la enfermedad de Gaucher. Es un desorden ligado a X, que causa deficiencia de α-galactosidasa, dando la acumulación de globotriaosilceramida (Gb3) dentro de los lisosomas de diversas células, lo que conduce a un deterioro renal, cardiaco y neurológico, que puede llevar a la muerte temprana. El análisis histológico renal, aplicado a un sistema de puntuación estandarizado, es útil para el inició de la terapia de sustitución enzimática y

* Corresponding author.
E-mail address: analauramenarodriguez@hotmail.com (A.L. Mena Rodríguez).

http://dx.doi.org/10.1016/j.hgmx.2016.08.010

Please cite this article in press as: Mena Rodríguez AL, et al. Histopathological findings in renal biopsies in Anderson–Fabry disease. Case series. Rev Med Hosp Gen Méx. 2016. http://dx.doi.org/10.1016/j.hgmx.2016.08.010

la evaluación del pronóstico. En este trabajo se clasificaron las lesiones histológicas encontradas en la microscopía de luz y la microscopía electrónica, en biopsias renales de pacientes con enfermedad de Fabry-Anderson, utilizando el Sistema de Puntuación de Patología Renal en Enfermedad de Fabry: Informe del Grupo Internacional de Estudio en Nefropatía de Fabry (ISGFN). Más de la mitad de los casos no presentaban alteraciones en la evaluación clínica y de laboratorio al momento de la biopsia, aun así, se encontraron cambios en la microscopía de luz y en la electrónica. La información proporcionada a través de la biopsia renal es un indicador temprano de daño renal, incluso sin datos de proteinuria y con función renal conservada.

Introduction

The metabolic defect in Fabry disease is a deficiency in the lysosomal hydrolase alpha-galactosidase A (alpha-Gal A), characterised by the hydrolytic excision of globotriaosylceramide (Gb3) and lyso-globotriaosylsphingosine (lyso-Gb3). Both Gb3 and lyso-Gb3 are elevated in male patients with classic Fabry disease, but may be only slightly increased or normal in late-onset or heterozygous variants.[8] The protein alpha-Gal A is coded by a gene at 12-kb on the long arm of the X chromosome (Xq22.1).[9] More than 400 mutations have been identified.[10,11] Most families have specific or private mutations and de novo mutations are rare.[6]

The disease's prevalence is estimated at 1:17,000 to 1:117,000 in Caucasian males. However, it is found in all ethnic and racial groups.[2,3] All males with the enzyme defect develop the disease, while female carriers are normally asymptomatic or express an attenuated form.[4,5] Kidney failure was the principal cause of death prior to the advent of dialysis treatment and the mean age of death was 41 years. Nowadays, dialysis and pharmacological antiproteinuric treatment have extended this to 55 years in 50% of homozygous patients.[6]

The Fabry Outcome Survey (FOS) and the Fabry Registry are international databases of patients with Fabry disease. An analysis of both reveals that the most common cause of death in 2001 was renal failure. In a recent study from 2001 to 2007, the authors reported that the most common cause of death was cardiovascular, at approximately 34% of male sufferers and 57% of female sufferers. This change in the principal cause of death appears to be due in particular to renal replacement therapy.[7]

The diagnosis is generally established by measuring alpha-Gal A activity in plasma or leukocytes in peripheral blood samples, fibroblast cultures, or by using dried blood spot samples on filter paper.[13] On the other hand, a diagnosis may initially be made through a renal biopsy taken to assess another type of chronic kidney disease (nephrotic syndrome, haematuria or other symptoms).[14,15] Nevertheless, although the histology may suggest the disease (zebra bodies), cases have been reported in which the changes observed under light and electron microscopy were indistinguishable from Fabry disease, but the lesions were caused by drugs (chloroquine, hydroxychloroquine, chlorphentermine, chlorcyclizine, imipramine, clomipramine, gentamicin and amiodarone), wherein the distinction was made using alpha-Gal A measurements.

The accumulation of Gb3 in the kidneys occurs first and foremost in the glomeruli (podocytes, endothelial and mesangial cells) as well as in the distal tubule. Morphological assessment using light and electron microscopes has revealed that glomerular and vascular changes occur in spite of normal kidney function.[16]

Glomerulosclerosis and fibrosis of the interstitial tubule are the histological characteristics that correlate most strongly with the progression of renal involvement, which translates to a need for renal replacement therapy (RRT). Kidney failure increases the risk of cardiovascular events.[1,7]

The drop in kidney function is related to the degree of proteinuria in untreated patients. Male sex and hypertension are also significant risk factors for the development of kidney failure.[17] As with any nephropathy, the protein overload can cause an increase in the levels of inflammatory mediators and interstitial accumulation of these mediators can lead to scarring of the kidneys.[18]

Proteinuria is an early sign of Fabry disease in both sexes and is the most frequent clinical manifestation.[2] Among patient in the FOS database, proteinuria was present in 44–54% of males and 33–41% of females. Similarly, the *Fabry Registry* recorded frank proteinuria (>300 mg/day) in 43% of males and 26% of females with stage I CKD; the rate was even higher in patients with more advanced renal involvement.[3]

A kidney biopsy is useful in all patients with any degree of proteinuria, albuminuria and/or renal dysfunction to assess the degree of glomerulosclerosis and interstitial damage due to its prognostic significance. In patients with minimal proteinuria and normal kidney function, a biopsy can also determine whether there are significant deposits of Gb3 (especially in podocytes and endothelial cells), reveal early damage indicating enzyme replacement therapy (ERT), or provide prognostic evidence, depending on the degree of glomerular sclerosis.[19] A biopsy may also be performed if there is the possibility of co-existing pathologies (for example, diabetes of other glomerular diseases, such as IgA nephropathy or thin basement membrane disease) and if there is a sudden inexplicable drop in kidney function[7].

An international study systematically classified renal histologic lesions in patients with Anderson–Fabry disease using

Please cite this article in press as: Mena Rodríguez AL, et al. Histopathological findings in renal biopsies in Anderson–Fabry disease. Case series. Rev Med Hosp Gen Méx. 2016. http://dx.doi.org/10.1016/j.hgmx.2016.08.010