FABRY DISEASE: EARLY AND SEVERE PRESENTATION IN WOMEN CARRIERS

CLINICAL NEPHROLOGY

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INTRODUCTION

Fabry Disease (FD) is a rare lisossomal X-linked disease that leads to alphagalactosidase A (alpha-Gal A) deficiency and accumulation of globotrialosilceramida (Gb-3). It causes cellular disfunction and several clinical abnormalities. In the kidney, the lesion are due to the accumulation of glycosphingolipids primarily in epithelial cells of the glomerulus and of the distal tubules. In later stages, and to a lesser degree, proximal tubules, interstitial histiocytes and interstitial cells may show lipids accumulation. The renal blood vessel are involved progressively. Other histologic changes in the kidney are severe arteriolar sclerosis, glomerular atrophy and fibrosis.

DISCUSSION

Recent evidences points that women in heterozygosis are potential patients and not only carriers of the new mutation. These patients can present the disease as severe as men, although the progression can be slower. In this case series, the average age of diagnosis was about ten years earlier than literature reports and already with important renal lesions, despite absence or mild proteinuria.

CASE PRESENTATION

From a male index patient with FD in hemodialysis was possible to diagnose, after genotyping, 8 female carriers (mother, 3 sisters, 2 daughters and 2 nieces of the index case). The genetic investigation shows the mutation p.G35V in homozygosity in exon 1, not already described in literature and with unknown clinical effect. The oldest one, with 71y (mother of the case index), died of mesenteric ischemia two months after diagnosis. The average age at diagnosis was 31y. Only one of the patients, the daughter of the index case is oligosymptomatic. The other 6 patients had characteristic symptoms such as headache, hypoacusia and acroparesthesia. They were screened for kidney disfunction (proteinuria and serum creatinine). They all had normal serum creatinine, 4 of them already have proteinuria > 150mg/24hours and < 1,0 g/24 hours but 3 of them didn□ t have proteinuria or albuminuria. They underwent percutaneous kidney biopsy with optic, electron microscopic and immunofluorescence avaliation. The histopathology analysis identified deposits of Gb-3 in the podocytes in all samples and signs of tubular atrophy and interstitial fibrosis in one patient with gross proteinuria (niece with 680 mg/24 hours). The results of laboratorial tests and kidney biopsy are showed below (tabel 1). It was also noted that this new mutation has a more aggressive neurologic involvement, reaching central and peripheral nervous system and aggressive kidney involvement showing that renal lesions evidenced in renal biopsy preceding the laboratory changes. Four of these patients already started enzymatic replacement therapy.

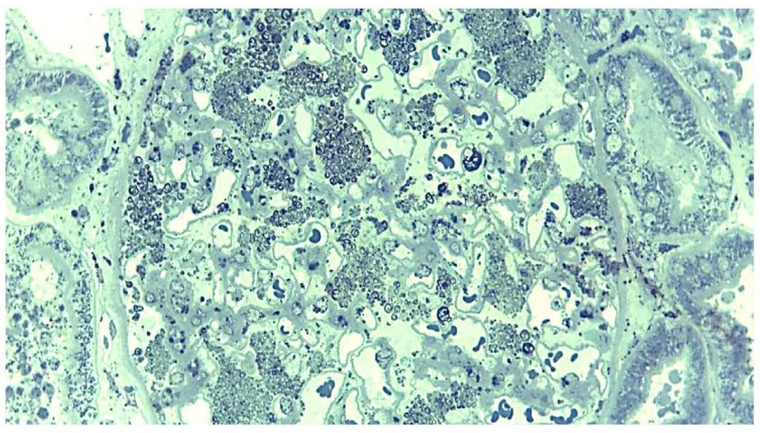

Figure 1

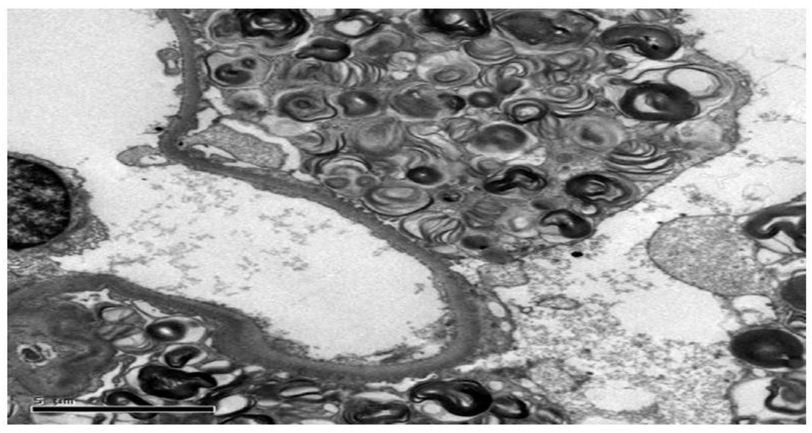

Figure 2

CONCLUSIONS

As FD presents an important decrease in quality of life and important organs dysfunctions, the early detection is crucial and a big challenge. Fabry nephropaty in women may be remarkable even before clinical and laboratorial signs, making the kidney biopsy essential in patients without proteinuria/albuminuria. The main point is to find out the correct time to start treatment, avoiding serious complications.

REFERENCES

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Tabel 1: Laboratorial and histopathologic findings in patients with Fabry disease from a single family. GFR: glomerular filtration rate. CKD-EPI: chronic kidney disease epidemiology collaboration

Patient, age (years)	1, sister, 49y	2, sister, 49y	3, sister, 47y	4, niece, 30y	4, niece, 27y	5, daughter, 22y	5, daughter, 16y
Creatinine (mg/dl)	0,7	0,9	0,9	0,9	0,7	0,8	0,9
GFR (mL/min) CKD-EPI equation	102	75	76	86	119	105	95
24-h urine protein and microalbumin (mg/24h)	280mg Not performed	140mg 21mg	220mg Not performed	150mg 9,8mg	680mg 480mg	120mg 5,7mg	60mg 2,8mg
Kidney biopsy findings - Light Microscopy (LM) - Immunofluorescence (IF) - Electron microscopy (EM)	LM: Vacuolization of the podocyte cytoplasm Focal tubular atrophy Mild interstitial fibrosis Mild arterial intimal hyperplasia. EM: Myelin-like inclusions and zebra bodies (ovoid inclusions) in podocyte cytoplasm	Not performed	LM: Vacualization of the podocyte cytoplasm Glomerular sclerosis Focal tubular atrophy Mild intersititial fbrosis Mild arterial intimal hyperplasia. EM: Myelin-like inclusions and zebra bodies (ovoid inclusions) in podocyte cytoplasm	LM: Diffuse microvacualization of the podocyte cytoplasm EM: Myelin-like inclusions in podocyte cytoplasm and endothelial cells	LM: Vacualization of the podocyte cytoplasm Glomerular sclerosis Focal tubular atrophy Mild intersititial fbrosis EM: Myelin-like inclusions in podocyte cytoplasm	LM: Diffuse degenerative alterations podocytes, microvacuolization of the podocyte cytoplasm (figure 1) EM: Myelin-like inclusions in podocyte cytoplasm, endothelial and tubular epithelial cells (figure 2).	LM: Diffuse degenerative alterations podocytes, microvacuolization of the podocyte cytoplasm, focal tubular atrophy, mild interstitial fibrosis EM: Myelin-like inclusions in podocyte cytoplasm endothelial cells and tubular epithelial cells

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H) Clinical Nephrology, primary and secondary glomerulonephritis.
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