FABRY DISEASE: RENAL INVOLVEMENT IN WOMEN IS MORE FREQUENT THAN EXPECTED

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INTRODUCTION

Fabry disease (FD) is an X-linked (Xq22.1) inborn error of glycosphingolipid catabolism resulting from deficient or absent activity of the lysosomal enzyme alpha-galactosidase A (a-gal-A). This enzymatic defect leads to the systemic accumulation of globotriaoslyceramide (Gb3) and related glycosphingolipids in the plasma and cellular lysosomes of vessels, nerves, tissues, and organs throughout the body. The disorder is a systemic disease, manifest as progressive renal failure, cardiac disease, cerebrovascular disease, small-fiber peripheral neuropathy, and skin lesions, among other abnormalities that reduce the expectation and quality of life. Practically, all men with a genetic mutation (homozygous) develop the disease, whereas women (heterozygous) present a wide variability in the severity of their phenotype, mainly due to random X-chromosome inactivation (Lyon hypothesis). Specifically, renal involvement is manifested by albuminuria, proteinuria, and progressive renal failure until renal replacement therapy is required. Like other rare diseases, it has been difficult to understand the natural progression of FD due to the scarcity of clinical information, especially in women.

PATIENTS AND METHODS

Descriptive, transversal and multicentric study. Thirty-five women were evaluated at the time of diagnosis of FD in three different centers of Argentina; Intensive Care Unit of the Dr. Enrique Erill Hospital from Escobar, Unit of Lysosomal Diseases of the Gamma Group from Rosario, and Center of Infusion and Study of Lysosomal Diseases of the Institute of Nephrology Pergamino.

The activity of the α-gal-A enzyme was determined on filter paper by fluorometric method and the mutational study by MLPA and sequencing.

Glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula in adult patients, and Schwartz formula in pediatric patients, using serum creatinine.

Pathological albuminuria was considered at values >20 ug/min in minuted urine or >30 mg/g creatinine in urine at random, and proteinuria at values >150 mg/d in at least two different samples in all cases. Glomerular hyperfiltration was defined as values greater than 125 ml/min/1.73 m², and the stages of chronic kidney disease (CKD) according to KDIGO guidelines.

RESULTS

Mean age was 26.6 years; 22 were adult women (over 18) and 13 were pediatric patients, with an average of 37.0 and 9.2 years respectively. Two index cases were detected; both adult women aged 28 and 55.

Seven different mutations of the GLA gene were found. The most frequent mutations were E398X and p.L415P. (Table 1).

Enzymatic activity of α-galA was performed in 27 (77.1%) patients, which was normal in 24/27 (89%).

25.7% (9/35) of the patients had a normal eGFR. The highest percentage (42.9%) showed glomerular hyperfiltration; 6 adults and 9 pediatric patients. CKD was detected in 11 patients (31.4%); with predominance of adult women [Fisher's test, p=0.0284]. We point out that of the adult patients 9 were G2 and 1 G3a, while the pediatric patient was in G2 stage of CKD. (Table 2).

Protein in urine was found in 16/35 patients (45.7%), with evident predominance of adult patients [Fisher's test, p=0.0125].

Albuminuria was detected in 12 adult patients and 1 pediatric patient (37.1%), and proteinuria in 2 adults and 1 young girl (8.6%). (Table 3).

Table 1 – Mutations

Mutation	Frequency	Percentage
E398X	14	40.0
p.L415P	11	31.4
A292T	4	11.4
R227Q	3	8.5
Del 3&4 exons	1	2.9
p.W81X	1	2.9
p.R301Q	1	2.9
Total	35	100

Table 2 – Glomerular Filtration Rate

	All patients	Adult	Pediatric
Normal GFR	9 (25.7%)	6	3
Hyperfiltration	15 (42.9%)	6	9
CKD	11 (31.4%)	10	1
Total	35 (100%)	22	13

Tabla 3 – Protein in urine

	All patients	Adult	Pediatric
Normal	19 (54.3%)	8	11
Albuminuria	13 (37.1%)	12	1
Proteinuria	3 (8.6%)	2	1
Total	35 (100%)	22	13

CONCLUSIONS

Although it is known that advanced renal involvement is more frequent in males, our results show a high percentage of women with signs of early renal damage at the time of diagnosis of FD; hyperfiltration as glomerular compensation, albuminuria, proteinuria and CKD.

In conclusion, we can say that women with FD may have a higher than expected organic compromise, with reduction in quality of life and risk of premature death. They should be evaluated periodically to determine the timing of enzyme replacement therapy initiation, which must be early without waiting for advanced organic damage.

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