Original Article

Direct Correlation between Age at Diagnosis and Severity of Nephropathy in Fabry Disease Patients

Abstract

Introduction: Nephropathy is one of the major complications of Fabry disease and mainly includes reduced glomerular filtration rate and proteinuria. Affected patients show different degrees of annual loss of renal function according to the magnitude of proteinuria and decrease in estimated glomerular filtration rate (eGFR) at the baseline. **Objetive:** To analyze the relationship between age at diagnosis and severity of nephropathy in a Fabry disease population. **Methods:** Cross-sectional design with retrospective data collection. **Results:** Seventy-two patients were studied with mean age of 26.26 ± 16.48 years and 30 men (41.6%). Twenty-seven paediatric patients and 45 adults were included. Thirteen genotypes were found: E398X, L415P, c886A>G, L106R, c.680G>A, A292T, c. 448.delG, R363H, C382Y, R301Q, D109G, del 3 and 4 exons, W81X, all pathogenic mutations of *GLA* gene. The mean eGFR in paediatric population was 115.81 ± 20.87 ml/min/1.73 m^2 and in adults was 80.63 ± 42.22 ml/min/1.73 m^2. The Pearson's bilateral correlation coefficient test (value = −0.462) between the age at diagnosis and eGFR indicates inverse correlation between both variables with a strong statistical significance (P = <0.01). Spearman's bilateral correlation coefficient (value = +0.385) between the variables at diagnosis and the degree of proteinuria indicates direct correlation between both variables with a strong statistical significance (P = <0.01). **Conclusions:** Diagnosis of Fabry disease patients at a younger age could be a key to improve the nephropathy prognosis and allow early and effective interventions.

Keywords: *Early diagnosis, estimated glomerular filtration rate, Fabry disease, nephropathy, proteinuria*

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Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by decreased or absent activity of lysosomal α-galactosidase-A (α-gal-A) activity, with progressive and multisystemic accumulation of globotriaosylceramide (Gb3) and its metabolites.[1] In the kidney, this accumulation is observed in glomerular cells, peritubular capillaries, vascular endothelial, smooth muscle cells, and tubular cells.[2,3] Progressive Gb3 accumulation is associated with life-threatening complications like renal failure, cardiovascular dysfunction, and stroke.[1,4] Nephropathy is one of the major complications of FD and mainly includes reduced glomerular filtration rate and proteinuria.[5]

Early diagnosis of nephropathy in FD patients is important. Prior to 2001, kidney disease was the major cause of death reported in affected patients.[6] Subsequently, it was described that life expectancy is decreased in FD patients of both sexes; the cardiovascular cause is the most frequent and patients who die by cardiovascular disease have two characteristics: (i) they previously received renal replacement therapy (RRT) for end-stage renal disease (ESRD) and, most importantly, (ii) they were diagnosed late.[7] In addition, affected patients show different degrees of annual loss of renal function according to the magnitude of proteinuria and the decrease in eGFR at the baseline.[8]

Enzyme replacement therapy (ERT) is a specific treatment for FD available since 2001. In Fabry nephropathy, its efficacy is greater the earlier it starts, a reduction of Gb3 tissue accumulation has been shown in a dose-dependent manner.[9] In more advanced stages of renal damage, its efficacy decreases due to the inability of correcting the progression when irreversible histological lesions are present, such as tissue fibrosis.[10,11]

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The aim of this study is to analyze the relationship between age at diagnosis and the severity of nephropathy in an FD population.

Subjects and Methods

In this retrospective study, patients with FD diagnosis were included from June 2007 to September 2017 from three reference centers in Argentina: (i) Los Manantiales Neuroscience Center, Grupo Gamma Rosario, Rosario, Santa Fe, Argentina; (ii) Center of Infusion and Study of Lysosomal Diseases of the Pergamino Clinical Nephrology Institute, Pergamino, Buenos Aires, Argentina; (iii) Intensive Unit Care of the Dr. Enrique Erill de Escobar Hospital, Belén de Escobar, Buenos Aires, Argentina. The diagnosis of FD was made by assessing enzyme activity α-gal-A[12] and molecular study.[13] Plasma and urine creatinine was determined by electro-chemiluminescence Roche Diagnostics. eGFR was calculated with Schwartz equation and CKD-EPI in patients under and over 18 years old, respectively.[14] To classify the eGFR stage The Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline 2013 (KDIGO) classification was used.[15] The albumin/creatinine ratio (ACR) in urine was used to estimate the urinary excretion of proteins in 24 h. Values from 0 to 30 mg/dl was considered normal, 30 to 300 mg/dl was indicative of albuminuria, and greater than 300 mg/dl indicated proteinuria, in at least two different samples of urine in all cases.

To estimate the degree of correlation between age and eFGR, the Pearson correlation coefficient was used. To estimate the degree of correlation between age and degree of proteinuria (ordinal with less than five categories), the Spearman correlation coefficient. It worked with a confidence interval (CI) of 95%. *P* values of <0.05 were considered of statistical significance to reject the null hypothesis.

The data were processed in IBM SPSS version 20 database. The study was approved by a local Ethics Committee. The adult patients signed an informed consent, and for the pediatric patientstheir legal representative gave consent according to local legislation.

Results

Seventy-two patients were studied with mean age of 26.26 ± 16.48 years and 30 men (41.6%). Twenty-seven pediatric patients and 45 adults were included. Thirteen genotypes were found: E398X, L415P, c886A>G, L106R, c.680G>A, A292T, c. 448.delG, R363H, C382Y, R301Q, D109G, del 3 and 4 exons, W81X, all pathogenic mutations of *GLA* gene.

The mean eGFR in paediatric population was 115.81 ± 20.87 ml/min/1.73 m^2 and in adults was 80.63 ± 42.22 ml/min/1.73 m^2. The mean ACR was 11.18 ± 11.10 mg/g and 386.63 ± 737.01 mg/g in paediatric patients and adults, respectively.

The FD complications frequency in studied population is shown in Table 1.

Table 2 shows the inverse correlation between the age at diagnosis and eGFR in Pearson's coefficient test (value = −0.462; *P* = <0.01), and Figure 1 shows the graphical representation of its linear correlation. Table 3 shows the direct correlation between age at diagnosis and degree of proteinuria in Spearman's coefficient (value = +0.385; *P* = <0.01).

Table 1: Frequency of typical Fabry disease complications in studied population

	Pediatric	Adults
Gender (M/F)	11/16	18/27
Cornea verticillata (%)	29.62%	31.11%
Gastrointestinal discomfort (%)	18.51%	28.88%
Neuropathic pain (%)	40.74%	73.33%
Angiokeratomas (%)	29.92%	42.22%
Deafness (%)	7.40%	44.44%
LVH (%)	0.00%	44.445
Arrhythmia (%)	11.11%	11.11%
CNS damage* (%)	7.40%	31.11%
Albuminuria/proteinuria (%)	22.22%	57.77%
eGFR decreased** (%)	0.00%	26.66%

*Stroke and/or typical lesions in cerebral white substance in angionuclear magnetic resonance of brain. **eGFR <60 ml/min/m^2. Ref: M: Males, F: Females, LVH: Left ventricular hypertrophy, CNS: Central nervous system, eGFR: Estimated glomerular filtration rate

Table 2: Pearson's bilateral correlation coefficient test between age at diagnosis and estimated glomerular filtration rate variables

		Age at diagnosis	eGFR
Age at diagnosis	Pearson correlation	1	−0.462**
	Significance (bilateral)		0.000
	n	72	72
eGFR	Pearson correlation	−0.462**	1
	Significance (bilateral)	0.000	
	n	72	72

**The correlation is significant at the 0.01 level (bilateral). eGFR: Glomerular filtration rate

Table 3: Spearman's bilateral correlation coefficient between the age at diagnosis and degree of proteinuria variables

		Age at diagnosis	Proteiuria
Rho of Spearman			
Age at diagnosis	Correlation coefficient	1.000	0.385**
	Significance. (bilateral)		0.001
	n	72	72
Proteinuria	Correlation coefficient	0.385**	1.000
	Significance. (bilateral)	0.001	
	n	72	72

**The correlation is significant at the 0.01 level (bilateral)

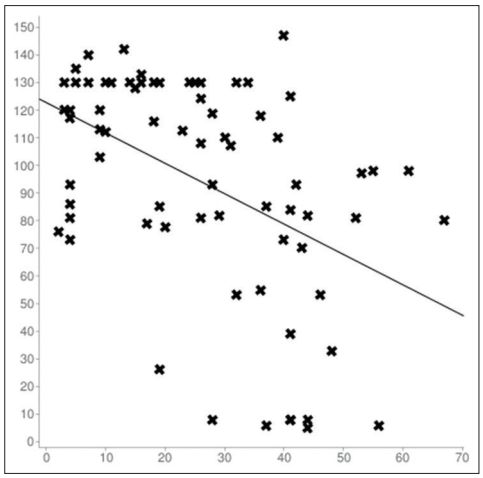

Figure 1: Linear correlation between age at diagnosis and eGFRvariables. Sample size: 72; Mean x ($\bar{x}$): 26.263888888889; Mean y ($\bar{y}$): 93.825; Intercept (a): 122.67968223109; Slope (b): −1.0986446962655; Regression line equation: y = 122.67968223109-1.0986446962655x. Ref: X axis: age (in years); Y axis: eGFR (in ml/min/m²)

Discussion and Conclusions

Nephropathy is a major complication of FD patients,[1,5] with a related increased morbidity and mortality .[7] Kidney damage can begin at a very young age,[16] and glomerular-sclerosis and vascular lesions have been described in renal biopsies of children and adolescents who had not yet exhibited decreased eGFR or overt proteinuria.[2,9,17-19]

In the natural course of Fabry nephropathy, the annual decline in renal function over time is related to the degree of proteinuria, male sex, and is faster when the initial eGFR is less than 60 ml/min/1.73 m^2.[4,8] Progression of renal damage culminates in ESRD. Affected males with "classical" mutations of the *GLA* gene, which produces severe decrease in α-gal-A activity, require RRT for ESRD treatment at ages of 35–44 years.[20] Therefore, the severity of the nephropathy conditions the evolution of FD patients, and the search for factors of poor renal prognosis is useful in affected patients.

Early biomarkers of prealbuminuric-stage nephropathy have been studied in FD patients with promising results,[21,22] because it is known that urinary protein excretion is present when the renal tissue lesions are irreversible.[2,9,16-19] The purpose of these investigations is to detect early renal damage before irreversible structural damage occurs in renal tissue.

The prototype of irreversible renal damage is renal fibrosis, both in glomerulosclerosis or tubulo-interstitial fibrosis.[10] Renal fibrosis, characterized by excessive deposition of extracellular matrix (ECM), is recognized as a common pathological feature of chronic kidney diseases (CKD), which is in direct relation to progression and leads to the development of ESRD.[23] As in other causes of nephropathy, there are no effective treatments that can reverse renal fibrosis in FD. In our study population, a direct relationship was found between age at diagnosis of FD and the severity of the nephropathy, as determined by eGFR and the degree of proteinuria.

The Pearson's bilateral correlation coefficient test (value = −0.462) between the age at diagnosis and eGFR indicates inverse correlation between both variables with a strong statistical significance (P = <0.01). At higher age, patients present with lower eGFR. On the other hand, the Spearman's bilateral correlation coefficient (value = +0.385) between the age at diagnosis and the degree of proteinuria indicates direct correlation with a strong statistical significance (P = <0.01). At higher age at diagnosis, patients have higher proteinuria.

ERT is more effective the earlier it is started; in a dose-dependent manner it is able to revert tissue lesions, even in injured podocytes.[9] In more advanced stages of nephropathy, ERT is less effective because it is unable to reverse renal fibrosis.[9,10,24,25]

In conclusion, the diagnosis of FD at a younger age could be a key to improve the prognosis of nephropathy and allow early and effective interventions.

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Conflicts of interest

There are no conflicts of interest.

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