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Prevalence of chronic kidney disease in fabry disease patients: Multicenter cross sectional study in Argentina

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ABSTRACT

Nephropathy is one of the major complications of Fabry Disease (FD) and mainly includes reduced glomerular filtration rate (GFR) and proteinuria. Despite the frequency, scarce information exists regarding the frequency of CKD as well as other related complications in FD patients in Argentina. The aim of the study was to measure the prevalence of CKD at diagnosis of FD as well as to describe other related conditions in a large cohort of patients with FD. **Methods**: a cross-sectional study performed in three FD centers of Argentina during January 2014 and January 2016. Information at diagnosis regarding patient demographics, disease characteristics, key laboratory values, and renal, cardiac, cerebrovascular diseases and other related complications were collected. **Results:** A total of 60 patients were included. The mean age at diagnosis was 25.5 ± 16 years. 42% of included patients presented CKD in which the disease was mild (GFR ≥ 60 and < 90) in 60% (n = 15), moderate (GFR ≥ 30 and < 60) in 16% (n = 4), severe (GFR ≥ 15 and < 30) in 4% (n = 1) and failure (GFR < 15) in 20% (n = 5). Arrhythmias were reported for 13.3% of patients. In 33.3% the echocardiographic evaluation demonstrated left ventricular hypertrophy and peripheral neuropathy in 63.3%. **Conclusion**: This study presents information regarding the prevalence of CKD in a large cohort of FD patients at the moment of diagnosis in Argentina. Future studies will help us to confirm these initial findings.

1. Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder due to alpha-galactosidase A (α-GalA) deficiency [1]. This deficiency causes the progressive accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids, particularly in vascular endothelial cells, renal cells and cardiomyocytes [1].

The "classic" severe phenotype, including systemic involvement, has an estimated incidence of 1 in 117,000 per year in the general population [1].

Nephropathy is one of the major complications of FD. Biopsies reveal GL-3 accumulation in tubular epithelial cells and in glomerular and endothelial cells, with focal and global glomerulosclerosis as early as in the second decade of life and even in pediatric patients [2–7]. The major signs of Fabry nephropathy include reduced glomerular filtration rate (GFR) and proteinuria [1,3,8], and affected males typically progress to End Stage Renal Disease (ESRD) by the fourth decade of life [9].

Despite the frequency of the disease and its consequences, in Argentina and in the South American region, scarce information exists regarding the frequency of CKD as well as other related complications in FD patients.

In order to better understand the burden of the disease, the aim of the study was to measure the prevalence of CKD at diagnosis of FD as well as to describe other related conditions in a large cohort of patients followed in three centers of Argentina.

2. Methods

2.1. Patients

We performed a cross-sectional study in three FD centers of Argentina during January 2014 and January 2016. The three centers included were: Critical Care Unit, Hospital Dr. Enrique Erill, Escobar City, Buenos Aires State; Lysosomal Disease Unit, Neurosciences Center Los Manantiales, Gamma Group, Rosario City, Santa Fe State; and

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Infusion Center of Lysosomal Diseases, Nephrology Institute of Pergamino, Buenos Aires State. All patients with confirmed FD followed at each center were included in the study. Diagnosis of FD was made by experienced clinicians for patients presenting clinical signs or familial history of the disease, with a biological confirmation (α-galactosidasa-A activity) through genetic analysis of the α-galactosidasa-A gene.

The study was approved by each local committee, and written informed consent after oral information was obtained in patients ≥ 18 years while, in patients under 18 years, written informed consent was obtained from patients and relatives.

2.2. Data collection

Once patients, guardians or next of kin consented, medical records were obtained. All available pre-defined clinical data were abstracted onto specific case report forms. The abstracted information at diagnosis included patient demographics and disease characteristics, key laboratory values, and renal, cardiac, cerebral vascular diseases and other related complications. Patient names remained blinded. Duplicate patient data obtained at more than one site were identified, and patient records were merged.

2.3. Outcome measures

2.3.1. CKD definition

CKD included chronic renal insufficiency or failure and proteinuria. End-stage renal disease (ESRD) was defined by a requirement for chronic dialysis or transplantation. CKD was categorized in stages based on GFR (kidney damage with mild reduction of GFR 60–89 mil/min; kidney damage with moderate reduction of GFR 30–59 ml/min; kidney damage with severe GFR 15–29 ml/min; and End Stage Renal Disease: kidney failure < 15 ml/min or dialysis). Available serum creatinine values at diagnosis were used to calculate GFR and defined CKD.

2.3.2. Cardiac events

Events at diagnosis included any type of arrhythmia (bradyarrhythmias, ventricular arrhythmias, supraventricular arrhythmias, premature [extra] beats) and ventricular hypertrophy determined in both cases by ECG and echocardiography.

2.3.3. Cerebrovascular events

These included stroke or transient ischemic attacks (TIA) classified by vascular territory or by amaurosis fugax.

2.3.4. Other clinical data

2.3.4.1. Gastrointestinal events. Gastrointestinal (GI) events were defined by the presence of postprandial abdominal pain, bloating, diarrhea, nausea, vomiting, early satiety or difficulty gaining weight. To consider GI events, symptoms must have been present at diagnosis. Other possible causes of symptoms were excluded in order to be considered as GI events related to FD.

2.3.4.1.1. Peripheral neuropathy and angiokeratomas. These were defined by the presence of discomfort of the hands and feet, with paroxysmal burning pains of the palms and soles.

The presence of cutaneous vascular lesions (angiokeratomas) was also evaluated in patients included at diagnosis.

2.3.4.2. Mutational analyses. Genomic DNA was isolated from blood collected in EDTA, and the GLA exons and adjacent intronic and promoter regions were sequenced using standard techniques.

2.3.4.3. Statistical analysis. Analysis was performed using STATA version 10.1 (Stata Corporation, TX, USA).

Baseline characteristics of the patients evaluated were reported as percentages for categorical data and mean with its standard deviation (SD) for continuous data.

3. Results

3.1. Patient population

A total of 60 patients were included. The mean age at diagnosis was 25.5 ± 16 years (range 2–67 years). In 16.7% the case was an index case and 58.3% of included patients were females. Characteristics of included patients, including mutational analysis, are presented in Table 1.

3.2. Fabry nephropathy

3.2.1. Estimated glomerular filtration rate

Baseline serum creatinine values were obtained for all patients. A total of 44.8% of patients presented albuminuria at diagnosis, while 22.4% presented proteinuria. Almost 42% of included patients presented CKD in which the disease was mild (GFR ≥ 60 and < 90) in 60% (n = 15); moderate (GFR ≥ 30 and < 60) in 16% (n = 4); severe (GFR ≥ 15 and < 30) in 4% (n = 1); and End Stage Renal Disease–ESRD- (GFR < 15) in 20% (n = 5). A total of 10% were receiving dialysis at the moment of diagnosis. The other nephropathy conditions related to Fabry in patients included at diagnosis are presented in Table 2.

3.2.2. Cardiac and cerebrovascular events

Cardiac events are summarized in Table 3. Arrhythmias were by far the most common cardiac event and were reported for 13.3% of patients. In 33.3% the echocardiographic evaluation demonstrated left ventricular hypertrophy, and no patients showed evidence of heart failure at the moment of inclusion in the study. Cerebrovascular events, including TIAs and strokes, were present in 20% of patients (Table 3).

3.2.3. Related conditions

GI events were present in 23.3% of included patients, peripheral neuropathy in 63.3% and angiokeratomas in 36.6% (Table 3).

4. Discussion

This study shows information regarding the prevalence of CKD in a large cohort of FD patients at the moment of diagnosis. A total of 42% of patients displayed CKD in which severe and ESRD was present in 10% of included patients. A total of 2.2% of patients received renal transplantation at the moment of the analysis, and almost 60% of patients had peripheral neuropathy. We also observed that arrhythmias were by far the most common cardiac event reported for 13.3% of patients, and in 33.3% the echocardiographic evaluation demonstrated left ventricular hypertrophy. Cerebrovascular events included TIAs and strokes were present in 20% of patients.

Our results are in line with previous studies, particularly the frequency of arrhythmias and cardiovascular events in affected patients. In the Fabry Registry, 33 of 287 patients with overt proteinuria had nephrotic syndrome at diagnosis of FD [10]. A small number of patients with severe CKD or ESRD (4 of 49) did not have overt proteinuria [10]. These data might not be representative of patients with mild to moderate FD, since these individuals are typically underrepresented in registries. Kampmann et al. reported that left ventricular hypertrophy occurs in up to 50% of males and one-third of females [4]. In most cases, left ventricular hypertrophy was concentric; however, an asymmetrical variety with septal thickening and posterior wall fibrotic thinning was present in an advanced stage of the disease. In other research, Yousef et al. reported that arrhythmias (including atrial fibrillation and ventricular tachycardia) occurred in 27–42% of male and 27% of female patients with FD [11]. In a recent study from the FD registry, results demonstrated that the most common type of reported severe events on ERT among male patients was cardiac, followed by

renal, and less frequently, stroke and no cardiac death; in females it was cardiac, followed by stroke and renal events [12]. Moreover, the occurrence of severe events was associated with an older age at initiation of ERT, whereas a pre-ERT history of events appeared to have a greater impact on residual risk in females than in males (pre-ERT: 8% of males, 7% of females). Comparisons with data from the general population suggests that cardiovascular events may occur more frequently in FD patients. Therefore, cardiac evaluation should be routinely performed in FD patients from the time of diagnosis of the disease.

In our study a high frequency of female patients and their renal involvement was found. Results are in line with Schiffmann et al. That reported in a cohort study that 15% of females had moderate and severe CKD and almost 50% of female patients with CKD had proteinuria [13].

Initial symptoms of FD, while reducing the quality of life, are not life-threatening and mainly include angiokeratomas, neuropathic pain and gastrointestinal symptoms. From the second decade of life, the involvement of the brain, kidney and heart can develop life-threatening complications such as stroke, CKD (usually associated with proteinuria and progressive decrease of GFR), LVH, arrhythmias and heart failure [14,15]. The progression of nephropathy to an end stage renal disease results in the chronic need for renal replacement therapies such as dialysis or kidney transplantation. Renal involvement is more frequent and early in affected males than females, while cardiovascular events are the leading cause of death in patients with FD, reducing life expectancy in affected patients of both sexes [9]. Currently, enzyme replacement therapy (ERT) is the only specific treatment for FD available. The interventions have shown to reduce plasma levels and tissue accumulation of Gb-3.8,9; their effectiveness is higher in early stages of the disease because, as the patient progresses and irreversible damage is present, scarce therapies can be provided to reverse the damage [8,16,17]. This is why efforts should focus on early diagnosis of patients, when there are greater possibilities to modify the natural course of FD. It is also worth to mention from our study, that it describes a successful family screening initiatives in the centers performed. In the same line, Laney et al. in 2008, reported researchers experience with three family trees, in which almost five patients per each index case were diagnosed. This findings, showed the relevance of a detailed pedigree of the index case in order to identify other affected patients in the family [18].

Although this study was carefully conducted with predefined analysis of the medical records of patients seen at expert centers, there are several evident limitations to this study that must be acknowledged: a) incomplete documentation driven by the study design; b) the inclusion of only three reference centers; and c) the cross-sectional design of the study. Despite these considerations, this study nonetheless expands the existing knowledge of Fabry nephropathy and related conditions in a less well-known and described population.

In conclusion, this study aims to describe the frequency of FD nephropathy at the moment of diagnosis in a large cohort of affected patients from Argentina. Future studies will help us to confirm these initial findings.

Conflict of interest

Authors declare no conflict of interest regarding the research performed.

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References

[1] S. Bansil, B.S. Singhal, G.K. Ahuja, U. Ladiwala, M. Behari, R. Friede, S.D. Cook, Comparison between multiple sclerosis in India and the United States: a case-control study, Neurology 46 (2) (1996) 385–387.
[2] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 30.
[3] S. Park, J.A. Kim, K.Y. Joo, S. Choi, E.N. Choi, J.A. Shin, K.H. Han, S.C. Jung, S.H. Suh, Globotriaosylceramide leads to K(Ca)3.1 channel dysfunction: a new insight into endothelial dysfunction in Fabry disease, Cardiovasc. Res. 89 (2) (2010) 290–299.
[4] J.S. Shen, X.L. Meng, D.F. Moore, J.M. Quirk, J.A. Shayman, R. Schiffmann, C.R. Kaneski, Globotriaosylceramide induces oxidative stress and up-regulates cell adhesion molecule expression in Fabry disease endothelial cells, Mol. Genet. Metab. 95 (3) (2008) 163–168.
[5] C.R. Kaneski, D.F. Moore, M. Ries, G.C. Zirzow, R. Schiffmann, Myeloperoxidase predicts risk of vasculopathic events in hemizygous males with Fabry disease, Neurology 67 (11) (2006) 2045–2047.
[6] C. Tondel, L. Bostad, K.K. Larsen, A. Hirth, B.E. Vikse, G. Houge, E. Svarstad, Agalsidase benefits renal histology in young patients with Fabry disease, J. Am. Soc. Nephrol. 24 (1) (2013) 137–148.
[7] M.A. Pina, J.R. Ara, P.J. Modrego, F. Morales, J.L. Capablo, Prevalence of multiple sclerosis in the sanitary district of Calatayud, Northern Spain: is Spain a zone of high risk for this disease? Neuroepidemiology 17 (5) (1998) 258–264.
[8] L. Shu, J.L. Park, J. Byun, S. Pennathur, J. Kollmeyer, J.A. Shayman, Decreased nitric oxide bioavailability in a mouse model of Fabry disease, J. Am. Soc. Nephrol. 20 (9) (2009) 1975–1985.
[9] K.D. MacDermot, A. Holmes, A.H. Miners, Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males, J. Med. Genet. 38 (11) (2001) 750–760.
[10] M.H. Branton, R. Schiffmann, S.G. Sabnis, G.J. Murray, J.M. Quirk, G. Altarescu, L. Goldfarb, R.O. Brady, J.E. Balow, H.A. Austin Iii, et al., Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course, Medicine (Baltimore) 81 (2) (2002) 122–138.
[11] Z. Yousef, P.M. Elliott, F. Cecchi, B. Escoubet, A. Linhart, L. Monserrat, M. Namdar, F. Weidemann, Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis, Eur. Heart J. 34 (11) (2013) 802–808.
[12] M. Namdar, J. Steffel, M. Vidovic, C.B. Brunckhorst, J. Holzmeister, T.F. Luscher, R. Jenni, F. Duru, Electrocardiographic changes in early recognition of Fabry disease, Heart 97 (6) (2011) 485–490.
[13] R. Schiffmann, D.G. Warnock, M. Banikazemi, J. Bultas, G.E. Linthorst, S. Packman, S.A. Sorensen, W.R. Wilcox, R.J. Desnick, Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy, Nephrol. Dial. Transplant. 24 (7) (2009) 2102–2111.
[14] R. Dobrovolny, L. Dvorakova, J. Ledvinova, S. Magage, J. Bultas, J.C. Lubanda, M. Elleder, D. Karetova, M. Pavlikova, M. Hrebicek, Relationship between X-inactivation and clinical involvement in Fabry heterozygotes. Eleven novel mutations in the alpha-galactosidase A gene in the Czech and Slovak population, J. Mol. Med. 83 (8) (2005) 647–654.
[15] R.Y. Wang, A. Lelis, J. Mirocha, W.R. Wilcox, Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life, Genet. Med. 9 (1) (2007) 34–45.
[16] P.B. Deegan, A.F. Baehner, M.A. Barba Romero, D.A. Hughes, C. Kampmann, M. Beck, Natural history of Fabry disease in females in the Fabry outcome survey, J. Med. Genet. 43 (4) (2006) 347–352.
[17] S. Beer, J. Kesselring, High prevalence of multiple sclerosis in Switzerland, Neuroepidemiology 13 (1–2) (1994) 14–18.
[18] D.A. Laney, P.M. Fernhoff, Diagnosis of Fabry disease via analysis of family history, J. Genet. Couns. 17 (1) (2008) 79–83.