End-stage renal disease in patients with Fabry disease: natural history data from the Fabry Registry

Alberto Ortiz, Bruno Cianciaruso, Marta Cizmarik, Dominique P. Germain, Renzo Mignani, João Paulo Oliveira, Jacobo Villalobos, Bojan Vujkovic, Stephen Waldek, Christoph Wanner, and David G. Warnock

1Unidad de Dialisis, Fundación Jiménez Díaz, Universidad Autonoma de Madrid, Madrid, Spain, 2Department of Nephrology, University Federico II, Naples, Italy, 3Biomedical Data Sciences and Informatics, Genzyme Corporation, Cambridge, MA, USA, 4University of Versailles-Saint Quentin en Yvelines, Hôpital Raymond Poincaré, Garches, France, 5Department of Nephrology and Dialysis, Infermi Hospital, Rimini, Italy, 6Departments of Nephrology and Human Genetics, Faculty of Medicine, Hospital São João, Porto, Portugal, 7Central University of Venezuela, Luis Razetti School of Medicine, Department of Physiology, Caracas, Venezuela, 8Department of Internal Medicine, General Hospital Slovenj Gradec, Slovenj Gradec, Slovenia, 9Salford Royal NHS Foundation Trust, Manchester M6 8HD, UK, 10Division of Nephrology, Department of Medicine, University of Würzburg, Würzburg, Germany and 11Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence and offprint requests to: Alberto Ortiz, E-mail: aortiz@fjd.es

Abstract

Background. Fabry disease, an X-linked lysosomal storage disorder caused by deficiency of α-galactosidase activity, is associated with progressive loss of kidney function. This study was undertaken to characterize Fabry disease among patients who reached end-stage renal disease.

Methods. Data from 2712 patients in the Fabry Registry were analysed to identify clinical characteristics of patients who received renal replacement therapy (RRT) during the natural history period (i.e. prior to any enzyme replacement therapy).

Results. A total of 213 patients [186 of 1359 males (14%) and 27 of 1353 females (2%)] received RRT at a median age of 38 years in both males and females. Males who received RRT were diagnosed at a median age of 35 years, compared to 23 years for non-RRT males. Sixty-one males and 10 females were not diagnosed with Fabry disease until after they had received RRT. Compared to other Fabry Registry patients, a higher percentage of RRT patients also experienced either a serious cardiovascular event or a stroke. Ninety-two of 186 males who had RRT (50%) experienced a cardiac event or stroke, compared to 230 of 1173 non-RRT males (20%). Ten of 27 RRT females (37%) had experienced a cardiac event or stroke, compared to 226 of 1326 non-RRT females (17%). Patients who had RRT experienced cardiovascular events and strokes at earlier ages than did patients who had not received RRT, and most received RRT before having a cardiac event or stroke.
Conclusions. While all Fabry patients are at risk of cardiovascular events and strokes, patients with Fabry nephropathy who develop kidney failure appear to have concurrent involvement of other major organ systems. It is important that Fabry patients are diagnosed early and that their renal function is monitored carefully.

Keywords: chronic kidney disease; Fabry disease; genetic renal disease; kidney transplantation

Introduction

Fabry disease (OMIM #301500) is an X-linked lysosomal storage disorder caused by deficient or absent activity of the lysosomal enzyme α-galactosidase A. Insufficient activity of this enzyme causes the accumulation of glycosphingolipids with terminal α-galactosidic linkages, particularly globotriaosylceramide (GL-3), in various tissues and cell types [1]. Over time, this progressive accumulation of glycosphingolipids is associated with impaired organ function. The initial manifestations of classic Fabry disease, including neuropathic pain in the extremities, hypohidrosis, angiokeratomas and gastrointestinal discomfort, typically appear during childhood. Later in life, many patients develop life-threatening complications, including chronic kidney disease (CKD) progressing to end-stage renal disease, cerebrovascular disease and heart disease. While the signs and symptoms of Fabry disease are generally most severe among hemizygous males, many heterozygous females also exhibit serious clinical manifestations [2].

Progressive renal dysfunction is exhibited by both males and females with Fabry disease [3,4], and those who develop kidney failure require renal replacement therapy (RRT), either in the form of chronic dialysis or a kidney transplant. In 2001, enzyme replacement therapy (ERT) with recombinant human α-galactosidase became available to treat Fabry disease [5,6]. ERT effectively slows the progression of Fabry nephropathy, and it is most effective in Fabry patients who are in the early stages of kidney involvement [7–10]. Unfortunately, many patients have progressed to kidney failure, some before being diagnosed with Fabry disease and/or before ERT became available. Clinical characterization of Fabry patients who receive RRT will provide a better understanding of the progression and burden of disease in these patients.

Materials and methods

The Fabry Registry is an ongoing, observational database that compiles clinical and laboratory data on patients with Fabry disease. The Fabry Registry began enrolling patients and collecting data in April 2001. As of May 2, 2008, the Fabry Registry included 2712 patients with known ERT status. All patients with Fabry disease are eligible for enrolment regardless of age, gender, symptoms or whether they are receiving ERT from any commercial source. Patient and physician participation is voluntary. All patients provide informed consent through local Institutional Review Boards/Ethics Committees. Treating physicians determine the actual frequency of assessments according to patients’ individualized needs. A schedule of recommended clinical assessments is available at http://www.fabryregistry.com. Given the voluntary nature of reporting data, patients’ ages at clinical assessments and time intervals between assessments are variable. Data collected by physicians or their designees are submitted to the Fabry Registry for central processing. The data are reviewed for missing data points, incomplete information and discrepancies with previously submitted data. Designated ‘cut-off’ values are used to identify any reported dosing or laboratory data that are clearly erroneous (i.e. incompatible with attainable ranges), and these data are not included in the summaries of dosing and laboratory parameters. All data management and analysis occur in a validated computing environment.

ERT was defined by the Fabry Registry criteria as either receiving chronic dialysis (≥40 days) or receiving a kidney transplant. Cardiovascular clinical events were defined as myocardial infarction, arrhythmia, congestive heart failure, angina pectoris or significant cardiac procedures (e.g. pacemaker placement, bypass, stent placement, valve replacement, transplantation). Cerebrovascular clinical events were defined as stroke.

The Modification of Diet in Renal Disease (MDRD) simplified equation was used to estimate glomerular filtration rate (eGFR) from serum creatinine levels [11]. For patients ≤18 years old, the Schwartz formula was used to determine eGFR [12].

Statistical analyses

The Wilcoxon two-sample test was used to compare median age at diagnosis between patients who had RRT versus those who did not. The Kaplan–Meier method was used to calculate the age at which patients first experienced serious cardiovascular events (as defined below) or strokes [13]. Statistical analyses were performed using SAS statistical software version 8 (SAS Institute Inc., Cary, NC).

All Fabry Registry patients who had data available during the natural history period (i.e. prior to any ERT) were included in these analyses. Patients for whom ERT status was unknown (2% of all patients enrolled) were excluded from these analyses to ensure that all data were obtained prior to initiation of ERT.

Results

As of May 2, 2008, 186 of 1359 males (14%) and 27 of 1353 females (2%) in the Fabry Registry had received RRT during the natural history period. As shown in Table 1, 132 patients had received a kidney transplant, including 116 of 186 males (62%) and 16 of 27 females (59%). A total of 156 males (84%) and 18 females (67%) had received chronic dialysis, most of whom had hemodialysis. Eighty-six of 186 males (46%) and seven of 27 females (26%) had received both chronic dialysis and a renal transplant. Four males and two females received two kidney transplants.

The median age at first RRT was 38 years among both genders (Table 2). Males who received RRT were diagnosed at a median age of 35 years (Table 2), as compared to a median age of 23 years (N = 1156, range 0 to 81 years) among males who had not received RRT (P < 0.0001). There was no significant difference in median age at diagnosis among females who had RRT (35 years) versus females who did not have RRT (33 years, N = 1267, range 0 to 81, P = 0.23). A substantial proportion of patients (33% of males and 37% of females) were not diagnosed with Fabry disease until after they had received RRT. Thirty-five of the 213 Fabry Registry patients who received RRT had died as of May 2, 2008, including 32 of 186 males (17%) and 3 of 27 females (11%). The median time from first RRT to death was 11 years in males and 6 years in females. These and other demographic data are summarized in Table 2.

As shown in Figure 1, most patients received their first RRT between the ages of 25 and 45 years. Twenty-one of
213 patients (10%) received RRT before the age of 25 years, including four males and one female who required RRT during their teen years (ages 14 to 19 years). The incidence rates of first RRT in all 2712 Fabry Registry patients in the natural history population are shown in Figure 2. Within each age category, male Fabry patients exhibited a markedly higher incidence of RRT than females.

Among the 1359 males enrolled in the Fabry Registry, only 121 (9%) were over the age of 55 years at the time of these analyses.

A summary of patients' renal characteristics at baseline (i.e. patients' first available natural history data) and prior to RRT is shown in Table 3. Ninety-six of 127 males for whom data were available (76%) had baseline eGFR values below 60mL/min/1.73m2. Among the 24 males for whom corresponding eGFR data prior to their first RRT were available, the change in eGFR over time was $-7.6 \text{mL/min/1.73m}^2/\text{year}$. The median urinary protein ratio in males was 0.7 at baseline and 2.0 prior to the first RRT.

Twelve of the 15 females who had baseline eGFR data available (80%) had eGFR values below 60mL/min/1.73m2. Among the four females for whom corresponding eGFR data were available. Limited urinary protein data were available for females; the median ratio was 1.0 at baseline ($n = 3$).
Percentages were calculated based on the number of patients in each category.

Compared to other Fabry Registry patients, more patients who had developed kidney failure and received RRT had also experienced either a cardiac event (as described in Materials and methods) or a stroke, as shown in Table 4. Ninety-two of 186 males who had RRT (49%) had experienced a cardiac event or stroke, compared to 230 of 1173 non-RRT males (20%). Ten of 27 females who had RRT (37%) had experienced a cardiac event or stroke, compared to 226 of 1326 non-RRT females (17%). Kaplan-Meier estimates of time to first cardiac or stroke event among all untreated Fabry Registry patients show that patients who had RRT also experienced cardiac and stroke events at earlier ages, compared to patients who had not received RRT (Figure 3). The average age at which males received RRT was 39 ± 9.9 years (mean ± SD). The median age at which these males had a 50% probability of experiencing their first stroke or cardiac event was 49 years (95% confidence interval, CI: 47.8 to 51.3), which was significantly younger than that of Fabry Registry males who had not received RRT: 56 years (95% CI: 54.5 to 59.7), P < 0.001. The average age at which females received RRT was 40 ± 12.3 years (mean ± SD). The median age at which these females had a 50% probability of experiencing their first stroke or cardiac event was 57 years, compared to 67 years (95% CI: 64.7 to 68.9) for females who had not received RRT. This difference was not statistically significant (P = 0.16); a 95% CI was not calculated for females who had RRT, due to the small number who experienced cardiac or stroke events (10 of 27). In terms of current age, patients who had received RRT were substantially older than patients who had not received RRT (median 50 versus 36 years in males and 48 versus 43 years in females), as shown in Table 4. A cause of death was reported for 24 of the 35 deceased patients who had received RRT. Fifteen of the 24 patients with a known cause of death died from cardiovascular events (63%), and four of 24 died from stroke (17%).

Among the Fabry Registry cohort, most RRT patients who had multiple serious clinical events received RRT before having a cardiac event or stroke. Fifty-nine of the 92 males (64%) and seven of the 10 females (70%) who had RRT in addition to a cardiac event or stroke received RRT before they had a cardiac event and/or stroke. Accordingly, 36% of males and 30% of females who had multiple serious clinical events had a cardiac event or stroke before they received RRT. Among males, the median time from first RRT to first stroke was 5 years (n = 19), and the median time from first RRT to first cardiac event was 6 years (n = 46). Among the small number of females who had other clinical events after RRT, the median time from first RRT to stroke was 12 years (n = 2), and time from first RRT to first cardiac event was 3 years (n = 5).

The majority of patients [113 of 186 males (61%) and 17 of 27 females (63%)] received their first RRT prior to 2000, at which time ERT was not commercially available. Most of the Fabry Registry patients who received RRT were eventually treated with ERT, including 111 males (60%) and 14 females (52%). The median age at which ERT was initiated was 47 years for males and 46 years for females.

Preliminary analyses of genotype records in the Fabry Registry did not shed any light on the progression of Fabry nephropathy to kidney failure. There was no statistically significant difference at the age of first RRT between the following groups of mutations: point mutations (missense,
null
Fig. 3. Kaplan–Meier estimates of time to first cardiovascular event or stroke among males (A) and females (B) in the Fabry Registry. Data for patients who received RRT during the natural history period are shown in ‘grey’, and data for patients who had not received RRT are shown in ‘black’. Vertical dashed lines represent median age at which each group of patients had a 50% probability of experiencing a cardiovascular event or stroke.
come commercially available. Though the data included in these analyses were exclusively from untreated patients, data regarding the subsequent use of ERT were also collected. Many RRT patients eventually received ERT (60% of males and 52% of females); however, they had been untreated for most of their lives.

Over the past decade, considerable progress has been made towards understanding Fabry nephropathy. It is now known that proteinuria is a key prognostic indicator for renal disease progression in patients with Fabry disease [8–10,23]. Recommended guidelines have recently been established for treating nephropathy in adults with Fabry disease [24]. These include controlling proteinuria to <0.5 g/day, controlling blood pressure and hyperlipidaemia and initiating ERT at the first sign of kidney involvement (or at the time of diagnosis for patients with little or no residual α-galactosidase A activity) [24].

In summary, patients with Fabry nephropathy who develop kidney failure appear to have concurrent involvement of other major organ systems. Improved vigilance in this regard should reduce or postpone progression and need for dialysis or transplantation for patients with Fabry disease. Whether or not stabilization of kidney function with ERT and anti-proteinuric therapy will reduce the subsequent incidence of cardiovascular events is an important question that must be addressed in prospective analyses.

Acknowledgements. The authors would like to thank the many patients that have agreed to participate in the Fabry Registry as well as the physicians and research coordinators that have entered clinical data on these patients. We also acknowledge our colleagues at Genzyme Corporation (Cambridge, MA), Dana Beitner-Johnson, PhD, for assistance with statistical analyses.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part, except in abstract format. The Fabry Registry is sponsored by Genzyme Corporation. AO, DPCG, JPO, BV, SW, CW, and DGW serve on the Genzyme-sponsored Fabry Registry Boards of Advisors. SW and DGW have served as a paid consultant to Genzyme Corporation. JPO and SW have received speaking fees from Genzyme Corporation. JPO, SW, and DGW have received travel and research support from Genzyme Corporation. SW has received speaking fees and served as a paid consultant to Shire Corporation and has received research funding from Shire Corporation and Amicus Therapeutics.

References


Received for publication: 2.6.09; Accepted in revised form: 23.9.09