Available online at www.sciencedirect.com
ScienceDirect
Molecular Genetics and Metabolism 93 (2008) 112–128
Molecular Genetics and Metabolism
www.elsevier.com/locate/ymgme

Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry

William R. Wilcox [a,b,*], João Paulo Oliveira [c], Robert J. Hopkin [d], Alberto Ortiz [e], Maryam Banikazemi [f], Ulla Feldt-Rasmussen [g], Katherine Sims [h], Stephen Waldek [i], Gregory M. Pastores [f], Philip Lee [j], Christine M. Eng [k], Laszlo Marodi [l], Kevin E. Stanford [m], Frank Breunig [n], Christoph Wanner [o], David G. Warnock [p], Roberta M. Lemay [q], Dominique P. Germain [r,s]

[a] *Medical Genetics Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd. SSB, Los Angeles, CA 90048, USA*
[b] *Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA, USA*
[c] *Medical Genetics, Hospital São João, Porto, Portugal*
[d] *Cincinnati Children's Hospital, Cincinnati, OH, USA*
[e] *Fundación Jiménez Díaz, Madrid, Spain*
[f] *New York University, New York, NY, USA*
[g] *Department of Medical Endocrinology, Rigshospitalet, University of Copenhagen, Denmark*
[h] *Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*
[i] *Hope Hospital, Salford, Manchester, United Kingdom*
[j] *National Hospital for Neurology & Neurosurgery, London, United Kingdom*
[k] *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA*
[l] *Department of Infectious and Pediatric Immunology, Medical and Health Science Centre, University of Debrecen, Debrecen, Hungary*
[m] *Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH, USA*
[n] *Department of Medicine, Division of Nephrology, University Hospital, Würzburg, Germany*
[o] *University Hospital, Department of Medicine, Würzburg, Germany*
[p] *University of Alabama at Birmingham, Birmingham, AL, USA*
[q] *Biomedical Operations, Genzyme Corporation, USA*
[r] *Centre de référence de la maladie de Fabry et des maladies héréditaires du tissu conjonctif. Assistance Publique – Hôpitaux de Paris, Paris, France*
[s] *University of Versailles - St Quentin en Yvelines, France*

Received 29 August 2007; received in revised form 24 September 2007; accepted 24 September 2007
Available online 26 November 2007

Abstract

Fabry disease (FD) is an X-linked lysosomal storage disease caused by alpha-galactosidase A deficiency. The Fabry Registry is a global clinical effort to collect longitudinal data on FD. In the past, most ''carrier'' females were usually thought to be clinically unaffected. A systematic effort has been made to enroll all FD females, regardless of symptomology. Of the 1077 enrolled females in the Registry, 69.4% had symptoms and signs of FD. The median age at symptom onset among females was 13 years, and even though 84.1% had a positive family history, the diagnosis was not made until a median age of 31 years. Twenty percent experienced major cerebrovascular, cardiac, or renal events, at a median age of 46 years. Among adult females with estimated glomerular filtration rate (eGFR) data ($N = 638$), 62.5% had an eGFR <90 ml/min/1.73m^2 and 19.0% had eGFR <60 ml/min/1.73 m^2. Proteinuria $\geqslant 300$ mg/day was present in 39.0% of females, and 22.2% had >1 gram/day. Quality of life (QoL), as measured by the SF-36® survey, was impaired at a later age than in males, but both genders experience significantly impaired QoL from the third decade of life onward. Thus, females with FD have a significant risk for major organ involvement and decreased QoL. Females should be regularly monitored for signs and symptoms of FD, and considered for enzyme replacement therapy.

* Corresponding author. Address: Medical Genetics Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd. SSB, Los Angeles, CA 90048, USA. Fax: +1 310 423 0620.
E-mail address: william.wilcox@cshs.org (W.R. Wilcox).

1096-7192/$ - see front matter
doi:10.1016/j.ymgme.2007.09.013

Keywords: Fabry disease; Heterozygote; Alpha-galactosidase A; Enzyme replacement; Chronic kidney disease; Proteinuria; Cardiomyopathy; Stroke; Quality of life; SF-36

Introduction

Fabry disease (FD, OMIM #301500) is an X-linked inborn error of metabolism characterized by decreased or absent activity of the lysosomal hydrolase α-galactosidase A (αGAL, E.C. 3.2.1.22), due to mutations in the gene that encodes the αGAL protein (GLA) [1,2]. Patients with this disorder are unable to effectively degrade membrane glycosphingolipids containing a terminal α-glycosidic galactose, especially globotriaosylceramide (GL-3), which consequently accumulates in various tissues. Deposition of GL-3 increases the risk for characteristic acroparesthesias of the hands and feet, angiokeratoma, strokes, hearing loss, myocardial microvascular ischemia and infarctions, arrhythmias, hypertrophic cardiomyopathy, valvular insufficiency, gastrointestinal symptoms, hypohidrosis, temperature and exercise intolerance, dysregulation of vascular tone and autonomic functions, obstructive lung disease, and chronic kidney disease leading to kidney failure [3–14].

FD causes significant morbidity and mortality in affected males. Acroparesthesias, fatigue, and gastrointestinal symptoms reduce emotional well being and productivity. Among males, proteinuria and progressive kidney disease are evident in the second to fifth decades of life [7]. Death occurs typically in the late fifth to early sixth decade from kidney failure, strokes and cardiac events [15].

As recently as 2001, most FD females were thought to be asymptomatic throughout a normal life span or to develop only minor manifestations of the disease [2]. However, several studies have since reported that heterozygous females do develop substantial symptoms of FD and are at risk of premature death [16–20].

Enzyme replacement therapy (ERT) with recombinant human α-galactosidase A (r-hαGAL) has been developed to treat FD [21,22]. Multiple studies have demonstrated that biweekly intravenous infusions of r-hαGAL effectively reduce plasma and tissue GL-3 accumulation [22,23], improve anhidrosis [24], peripheral nerve function [25], pulmonary gas exchange [26], gastrointestinal symptoms [27], acroparesthesias [21], and can stabilize kidney function [28–30]. Although relatively few women were included in these trials, ERT also appears to benefit females [31].

With an estimated incidence of 1:40,000 in males [2,32], FD is considered to be an "ultra-orphan" disease. However, screening studies have shown an incidence of 0.1–1% among male dialysis patients [33–36], 3–5% of "idiopathic" hypertrophic cardiomyopathy cases [37–39], and 4.9% of male (2.4% of female) patients with cryptogenic strokes [40]. Late onset forms with significant residual enzyme activity may be particularly common, up to 1:4600 in one study [41].

Like other rare diseases, it has been difficult to develop a clear understanding of the natural progression of FD due to the paucity of longitudinal clinical information, particularly on heterozygous females. The Fabry Outcomes Survey (FOS), a European registry of Fabry patients, reported symptoms and manifestations in more than 300 females [19]. The Fabry Registry (http://www.fabryregistry.com), created in 2001, has now collected detailed data on 1077 female patients with FD. We analyzed the data in the Fabry Registry to compare the age at symptom onset and at diagnosis, and the incidence of clinical events among male and female patients (i.e. prior to treatment with ERT).

Methods

Data analysis and statistics

The Fabry Registry is an ongoing, observational database that tracks the natural history and outcomes of patients with FD. All FD patients are eligible to enroll in the Fabry Registry, regardless of symptoms or whether or not they are receiving ERT. Patient and physician participation is voluntary. All patients provided informed consent and may decline to participate or withdraw consent at any time. Treating physicians determine the actual frequency of assessments according to a patient's individualized need for medical care and routine follow-up. However, there is a recommended schedule of clinical assessments for patients with FD (available at http://www.fabryregistry.com).

All data collected by the Fabry Registry are entered into a database through a set of standardized case report forms. All of the data used in these analyses are natural history data (i.e., prior to any treatment with ERT). Data analyses were performed using the SAS statistical software system version 8 [42] and summarized using descriptive statistics. Statistical comparisons between data from male versus female patients were made for certain key parameters, as indicated in the text. Given the sporadic nature of data reported to the Fabry Registry (i.e., different patients had clinical assessments at widely varying ages and time intervals), statistical comparison of these gender differences must be interpreted with caution. The 2-sample median test was used to compare the median age of Fabry symptom onset, median age at first stroke, and median age at first cardiac event between males and females. The 2-sample *t*-test for unequal variances was used to compare the mean age of neurologic pain onset and age at first reported left ventricular hypertrophy (LVH) between males and females. The Cochran-Mantel-Haenszel test was used to compare the percentage of males versus females with at least 1 event (cerebrovascular, cardiac, or renal), abdominal pain, diarrhea, and first symptom onset of neurologic pain. The Kaplan–Meier estimator (also known as the Product Limit Estimator) was used to estimate the time from birth to specific renal, cardiac, or stroke events with recorded dates through the final available natural history date in the Registry for each patient. Kaplan–Meier curves were calculated for time to any event for both males and females.

The Fabry Registry is owned and administered by Genzyme Corporation as part of their post-marketing regulatory commitments. There are currently 3 independent advisory boards that include physicians from a variety of specialties worldwide. The authors of this study represent a subset of the members of those 3 boards.