Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry

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Summary The Fabry Registry is a global observational research platform established to define outcome data on the natural and treated course of this rare disorder. Participating physicians submit structured longitudinal data to a central-confidential database. This report describes the baseline demographic and clinical characteristics of the first 1765 patients (54% males (16% aged <20 years) and 46% females (13% <20 years)) enrolled in the Fabry Registry. The median ages at symptom onset and diagnosis were 9 and 23 years (males) and 13 and 32 years (females), respectively, indicating diagnostic delays in both sexes. Frequent presenting symptoms in males included neurological pain (62%), skin signs (31%), gastroenterological symptoms (19%), renal signs (unspecified) (17%), and ophthalmological signs (11%). First symptoms in females included neurological pain (41%), gastroenterological symptoms (13%), ophthalmological signs (11%), and skin signs (12%). For those patients reporting renal progression, the median age at occurrence was 38 years for both sexes, but onset of cerebrovascular and...
cardiovascular events was later in females (median 43 and 47 years, respectively) than in males (38 and 41 years, respectively). This paper demonstrates that in spite of the considerable burden of disease in both sexes that begins to manifest in childhood or adolescence, the recognition of the underlying diagnosis is delayed by 14 years in males and 19 years in females. The Fabry Registry provides data that can increase awareness of common symptoms in all age groups, as well as insight into treated and untreated disease course, leading to improved recognition and earlier treatment, and possibly to improved outcomes for affected individuals.

### Abbreviations

- **CNS** central nervous system
- **ERT** enzyme replacement therapy
- **α-Gal A** α-galactosidase A
- **GL-3** globotriaosylceramide
- **HIPAA** Health Insurance Portability and Accountability Act
- **IRB/EC** Institutional Review Board/Ethics Committee
- **SD** standard deviation

### Introduction

Fabry disease (OMIM 301500) is a progressive, life-threatening, multisystemic, X-linked lysosomal storage disorder that affects primarily males, but may also cause significant morbidity in heterozygous females. The deficiency of the enzyme α-galactosidase A (α-Gal A, EC 3.2.1.22) causes accumulation of globotriaosylceramide (GL-3) and related glycolipids in tissues and body fluids. This initial insult leads to dysfunction of basic metabolic processes within cells, ultimately leading to cellular death, to secondary (inflammatory) processes, and to progressive vital organ dysfunction (Fig. 1) (Desnick et al. 2001; Eng et al. 2006). GL-3 accumulation affects many cell types, including vascular endothelium, various renal cell types, and epithelial and smooth-muscle cells of the cardiovascular and renal systems. Early symptoms result from disease progression in the somatosensory and autonomic nervous systems, while life-threatening complications occur later as a result of organ damage in the kidneys, heart and brain (Eng et al. 2006). Most male patients with Fabry disease have a markedly shortened lifespan with death occurring in the fourth or fifth decade of life. Heterozygous females experience a spectrum of disease severity, ranging from being essentially asymptomatic to having disease symptoms on par with classically affected males (Eng et al. 2006; MacDermot et al. 2001a,b).

Before the advent of enzyme replacement therapy (ERT), treatment for Fabry disease consisted of symptomatic management. ERT was evaluated in clinical trials during the late 1990s (Eng et al. 2001a,b; Schiffmann et al. 2000, 2001), leading to the commercial availability of agalsidase beta (Fabrazyme, Genzyme Corporation, Cambridge, MA, USA) and agalsidase alfa (Replagal, Shire Human Genetic Therapies, formerly Transkaryotic Therapies, Inc., Cambridge, MA, USA). Based on clinical trials, ERT is now considered standard of care for symptomatic male and female patients with Fabry disease (Desnick et al. 2003; Eng et al. 2006) and data regarding long-term clinical efficacy are emerging. The extended phase III study with agalsidase beta at 1 mg/kg every other week has shown that nearly all patients achieved complete clearance of GL-3 from various renal cell types (Thurberg et al. 2002, 2004; Wilcox et al. 2004). A randomized, placebo-controlled trial of agalsidase beta (1 mg/kg) demonstrated a significant reduction in renal, cardiac and CNS events in patients with moderately advanced Fabry disease (Banikazemi et al. 2007).

Although the clinical development of ERT has provided insight into many aspects of Fabry disease, a fuller understanding of the natural course, clinical characteristics and long-term effects of intervention in this rare metabolic disorder requires a prospectively obtained longitudinal database of clinical information.