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Fabry in the older patient: Clinical consequences and possibilities for treatment

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ABSTRACT

Baseline demographic and phenotypic characteristics of patients aged ≥50 years in the Fabry Outcome Survey (Shire; data extracted June 2014) were compared with younger adults to investigate potential factors influencing treatment decisions in later life. Age groups were defined using age at treatment initiation or at FOS entry for untreated patients: 18–49 (n = 1344; 49.5% male; 64.6% received agalsidase alfa enzyme replacement therapy [ERT]); 50–64 (n = 537; 35.4% male; 74.3% treated); 65–74 (n = 137; 32.1% male; 68.6% treated); and ≥75 years (n = 26; 26.9% male; 50.0% treated). Successive age groups showed higher median age at first symptom and diagnosis. Median alpha-galactosidase A activity, measured as percentage activity of the midpoint of the normal range, was much greater in females than males of all groups except ≥75 years (33.4% in females; 27.8% in males). Patients aged ≥75 years showed greater values than patients aged 18–49 years for median left ventricular mass indexed to height (62.7 vs 42.4 g/m$^{2.7}$), mean ventricular wall thickness (15.0 vs 10.0 mm) and prevalence of hypertension (57.7% vs 21.8%), and lower median estimated glomerular filtration rate (Modification of Diet in Renal Disease: 65.6 vs 98.5 mL/min/1.73 m^2). Larger proportions in the groups aged ≥50 exhibited cardiac and/or cerebrovascular manifestations compared with patients aged 18–49 years. The smaller proportion of patients receiving ERT aged ≥75 years compared with the younger groups might reflect relatively milder disease burden or physician/patient reluctance to initiate/continue ERT at this age. Further studies are needed to increase knowledge of Fabry disease and ERT in later life.

1. Introduction

Fabry disease results from a deficiency in lysosomal alpha-galactosidase A (α-Gal A) due to mutations in the *GLA* gene. This leads to the accumulation of globotriaosylceramide in cells and a multisystem pathology.

Despite Fabry disease being X-linked, female heterozygotes can experience all of the signs and symptoms of the disease, but generally later and with a milder, more variable phenotype than in males [1–4]. Females may, however, on occasions have a significant burden of disease, similar to that observed in males [5,6]. The overall life expectancy (calculated from birth) for patients with Fabry disease is 58 years for men and 75 years for women [7].

Two broad phenotypes of Fabry disease are now recognised, the classical form with childhood onset and multi-organ progression, and a later-onset phenotype with limited organ involvement presenting in middle age. In classical Fabry disease, α-Gal A activity is greatly diminished, at <1% of normal in males, whereas patients with later-onset cardiac or renal variants tend to have α-Gal A activity between 1% and 30% [8]. Diagnosis of the later-onset variant may be delayed due to lack of obvious external symptoms and signs such as acroparesthesia and angiokeratoma. In all Fabry disease phenotypes, the natural history of

Abbreviations: α-Gal A, alpha-galactosidase A; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FOS, Fabry Outcome Survey; LVH, left ventricular hypertrophy; LVMI, left ventricular mass indexed to height; MDRD, Modification of Diet in Renal Disease; MWT, mean ventricular wall thickness.

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aging may be difficult to distinguish from Fabry-specific complications, which themselves become more severe and prevalent with age.

Enzyme replacement therapy (ERT) in Fabry disease is expected to be most successful when started early in the disease course [9–11]; its initiation has been recommended as soon as early clinical signs of kidney, heart or brain involvement consistent with Fabry disease become apparent [12].

Family screening and symptom-based screening programmes have identified people with Fabry disease in later-life stages and it is unclear whether the rationale for starting treatment in this more advanced age group should be the same as for index cases diagnosed at a younger age. Symptom-based therapy in these older patients may be more beneficial, more cost effective and less burdensome to the health care provider than starting ERT to prevent Fabry disease progression and clinical events. Few studies focusing on elderly patients with Fabry disease have been performed; one analysis of six patients indicated limited benefit in starting/continuing ERT in elderly patients in terms of life expectancy and cost-effectiveness [13].

The objective of the present analysis was to describe the demographic and phenotypic characteristics of patients who were ≥50 years of age in the Fabry Outcome Survey (FOS) and to compare them with younger adult patients in an attempt to identify any factors that might influence the decision to treat, or not to treat, at later stages in life.

2. Methods

This was a retrospective analysis of data entered in FOS, a global, observational registry sponsored by Shire for the collection of outcomes data on Fabry disease. A diagnosis of Fabry disease is confirmed by reduced alpha-galactosidase A activity in plasma and leukocytes in males, and by molecular analysis to confirm *GLA* mutations in females and males. All patients with a confirmed diagnosis of Fabry disease who are receiving, or are eligible for ERT with agalsidase alfa, can be registered in FOS. Patients who are currently receiving ERT with a drug other than agalsidase alfa are not eligible for inclusion in FOS. Data collection in FOS was initiated in 2001, and all patients aged ≥18 years with data entered in FOS at the time of extraction (June 2014) were included.

The institution review boards of each participating centre approved FOS and all patients provided written informed consent prior to enrollment.

2.1. Populations analyzed

To analyze the presentation and clinical characteristics of elderly patients the population in FOS was divided into the following age groups: patients 18–49 years, 50–64 years, 65–74 years and ≥75 years (elderly group). The groups were stratified by age at treatment initiation for treated patients and age at FOS entry for untreated patients. Treated patients received agalsidase alfa 0.2 mg/kg body weight every other week.

2.2. Parameters evaluated

Patient demographics and the following baseline clinical characteristics were compared between the age groups: cardiac parameters (obtained via echocardiography, according to the American Society of Echocardiography recommendations) [14]: left ventricular mass indexed to height (LVMI), left ventricular hypertrophy (LVH; >48 g/$m^{2.7}$ in females and >50 g/$m^{2.7}$ in males), mean ventricular wall thickness (MWT), aortic root diameter; renal parameters: serum creatinine, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula, Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) equation, urine protein. Chronic kidney disease staging according to KDIGO guidelines [15] was performed for patients who had both eGFR and albumin data available (Supplementary data Fig. S1).

Baseline cardiac, renal, cerebrovascular and auditory signs/symptoms were also compared between the age groups of the overall population.

2.3. Statistical analysis

Descriptive statistics were calculated for all continuous and categorical variables to enable a thorough description of the demographic and clinical characteristics of patients aged ≥50 years.

3. Results

3.1. Enrollment and demographics

As of June 2014, a total of 2338 patients were enrolled in FOS (1279 females and 1059 males); 2044 of these were aged ≥18 years and are included in the current study. This study focuses on age rather than gender; however, data stratified by both age and gender are provided for reference in Supplementary data Tables S1–S4.

The proportion of females increased with successive age group (Table 1). The proportions of patients treated with ERT were 64.6% aged 18–49 years, 74.3% aged 50–64, 68.6% aged 65–74 and 50.0% aged ≥75 years (Table 1).

Median age at first symptom and diagnosis increased with each successive age group, whereas the median delay in diagnosis was similar between the groups aged 50–64 and 65–74 years (Table 1).

Median α-Gal A activity, measured as percentage activity of the midpoint of the normal range, was similar in females regardless of age, and generally much higher than in males. In the elderly group, α-Gal A activity was at its highest in males (27.8% [13.6–42.0%]) and thus closer to the level observed in females (33.4% [1.1–487.9%]; Table 1).

The largest proportion of Fabry disease diagnoses in each age group was made as a result of family members being affected. Of the specialists who first suspected Fabry disease, cardiologists diagnosed the largest proportions of patients in all groups aged ≥50 years. Nephrologists diagnosed the largest proportion of patients aged 18–49 years (Table 1).

The majority of patients were negative for heart pacemaker/transplant/defibrillator use at any time (Table 1). Therapy with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers was more prevalent in patients who were aged ≥50 years than in younger adults (Table 1). Diabetes mellitus was more prevalent in patients aged ≥50 years than in younger adults (6.1% aged 50–64; 10.9% aged 65–74 and 3.8% aged ≥75 years vs 1.4% aged 18–49 years), and hypertension prevalence decreased with decreasing age group (57.7% aged ≥75 years; 48.2% aged 65–74; 41.9% aged 50–64; 21.8% aged 18–49; Table 1).

3.2. Phenotypic characteristics

3.2.1. Baseline cardiac parameters and events

A higher median baseline LVMI was demonstrated by Fabry patients presenting at a more advanced age than in the youngest group (Fig. 1A). Similarly, median MWT was progressively higher in the older groups (Fig. 1B).

Median aortic root diameter was similar for each of the age groups (see Supplementary data Table S2 for aortic root diameter by gender).

The rate of cardiac events/manifestations experienced before treatment initiation or FOS entry was greater in patients aged >50 years, where similar rates were experienced by the groups aged 50–64 (81.0%) and 65–74 (80.3%), and the highest rate (88.5%) by the elderly group. Fewer patients experienced any cardiac event/manifestation in the youngest group (58.6%; Table 2). Left ventricular hypertrophy was the most prevalent cardiac manifestation in each age group (Table 2).