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Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey

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Abstract

Background Fabry disease is a rare X-linked disorder caused by deficient activity of the lysosomal enzyme α-galactosidase A. Progressive accumulation of the substrate globotriaosylceramide in cells throughout the body leads to major organ failure and premature death. In response to the recent introduction of enzyme replacement therapy, the Fabry Outcome Survey (FOS) was established to pool data from European clinics on the natural history of this little-known disease and to monitor the long-term efficacy and safety of treatment. This paper presents the first analysis of the FOS database and provides essential baseline data against which the effects of enzyme replacement can be measured.

Design Baseline data from a cohort of 366 patients from 11 European countries were analysed in terms of demography and clinical manifestations of Fabry disease.

Results Misdiagnosis of Fabry disease is common, and the mean delay from onset of symptoms to correct diagnosis was 13·7 and 16·3 years in males and females, respectively. Although previously thought to have serious manifestations only in hemizygous men, the FOS database has confirmed that females heterozygous for Fabry disease are similarly affected. Furthermore, signs and symptoms of Fabry disease may be present from early childhood.

Conclusions With the advent of enzyme replacement therapy, it is important that general practitioners and physicians in a range of specialties recognize the signs and symptoms of Fabry disease so that effective treatment can be given. Baseline data from FOS demonstrate that enzyme replacement therapy should not be restricted to hemizygous men, but should be considered for both heterozygous females and children.

Keywords Agalsidase alfa, enzyme replacement therapy, Fabry disease, outcomes database, pharmacoepidemiological survey.
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Introduction

Fabry disease is an X-linked lysosomal storage disorder associated with severe multi-organ dysfunction and premature death [1]. Despite the serious nature of Fabry disease, its rarity – estimated incidence of 1 in 40 000–117 000 live births for males [1,2] – and variable presentation mean that patients are frequently misdiagnosed and may spend years or even decades receiving inappropriate treatment.

Numerous, often private, mutations (i.e. occurring in only single or small numbers of families) are responsible for deficient activity of the enzyme α-galactosidase A in patients with Fabry disease [1,3–5]. The lack of enzyme activity results in the progressive accumulation of neutral glycosphingolipids, primarily globotriaosylceramide (Gb_3), within lysosomes of cells in various organ systems. This leads to the wide variety of progressive clinical manifestations in affected individuals. The common clinical features of Fabry disease include acroparaesthesia and pain crises, gastrointestinal symptoms, angiokeratomas and corneal dystrophy. Renal failure, cardiomyopathy and cerebrovascular disease lead to premature death, on average 15 years earlier in females [4] and 20 years earlier in males [3] compared with the general population. Previously, symptoms were thought to be rare and mild in female heterozygotes [1]. It is now known, however, that females can also be severely affected, although progression of the disease to organ failure generally occurs later in life and the symptom severity tends to be more variable than in males [4,6–8].

With the introduction of enzyme replacement therapy (ERT) [9], it is now possible to target the underlying cause of Fabry disease. Schiffmann *et al.* [10] and Eng *et al.* [11] have demonstrated tissue clearance of Gb_3 after infusion of agalsidase alfa and agalsidase beta, respectively. Furthermore, significant clinical improvements compared with placebo, including stabilization of renal function, have been demonstrated after 6 months of ERT with agalsidase alfa [12]. It may thus be possible to halt and perhaps even reverse the progress of Fabry disease before irreversible organ damage occurs. Early diagnosis of Fabry disease is therefore important, and clinicians in a range of specialties, as well as general practitioners, should be aware of the signs, symptoms and natural history of the disease. The advent of treatment also imposes the need for a more rigorous and complete assessment of the symptomatology and natural history of Fabry disease.

This paper describes the demographic and baseline clinical characteristics of the largest cohort of patients with Fabry disease ever studied. All the patients are enrolled in the Fabry Outcome Survey (FOS): a European outcomes database for all patients with Fabry disease who are receiving, or are candidates for, ERT with agalsidase alfa. FOS is not a postal questionnaire; data are entered into the database following a structured clinical assessment by a physician or a nurse specialist. Data from all consenting patients are entered, thereby minimizing bias. Nevertheless, mildly affected patients are less likely to be diagnosed and therefore less likely to be included in the database. Patients receiving agalsidase beta are not included. By pooling data on Fabry disease from different specialist centres, FOS enables the natural history of this rare disease to be studied in a large group of male and female patients and provides baseline data against which the effects of treatment with agalsidase alfa (Replagal™, TKT Europe – 5S, Danderyd, Sweden) can be measured.

Methods

Patients

The FOS database has been approved by the Ethics Institution review board of all participating centres, and all patients give written informed consent. At the time of this analysis, FOS contained baseline data on 366 patients (201 males, 165 females), of whom 241 (65·8%) were receiving ERT with agalsidase alfa at a dose of 0·2 mg kg^{-1} body weight intravenously every 2 weeks.

Data collection

On enrolment into FOS, each patient's medical history is documented by a physician or nurse specialist, including the year of diagnosis of Fabry disease, signs and symptoms of the disease, treatment, demographic details and family history.

All measurements performed routinely in clinical practice are entered into the database. Assessments of cardiac and renal function, and ophthalmological, gastrointestinal and audiological examinations are optional. FOS also offers participating physicians central measurements for the diagnosis of Fabry disease, DNA analysis and plasma and urinary Gb_3.

De-personalized data are submitted electronically by participating physicians to the central FOS database.

There have been several reports of milder late-onset variants of Fabry disease, with effects limited to the heart [13–16], kidney [17] or the heart and kidney [18]. The FOS database was therefore specifically examined for patients with renal or cardiac variants of the disease.

Data analysis

Student's two-sample and one-sample and Fisher's exact tests were used for statistical analyses.

Role of the funding source

Data collection and analysis in FOS are supported by TKT Europe – 5S. The sponsor had no role in the interpretation of data or writing of the report.

Results

Patient demographics

Characteristics of the 366 patients in the cohort studied are given in Table 1. Patients were recruited from 11 European countries (Germany, 25%; Czech Republic, 16%; UK, 12%; Switzerland, 12%; Italy, 11%; Belgium, 7%; Spain, 7%; Sweden, 6%; Austria, 3%; France, 1%; Norway, 1%). In most countries, the numbers of male patients exceeded those of females; however, in the Czech Republic and Germany, there were more females than males (Germany, 53 vs. 38; Czech Republic, 33 vs. 24). Overall, 55% of patients were males and 45% females. Females were significantly older than males (females, 41·4 ± 17·1 years; males, 35·5 ± 13·1 years; $P < 0·001$).

Diagnosis of 'index cases'

Of the 366 patients in the database, 268 had not been diagnosed as a result of having an affected family member. Data on age at onset of symptoms and age at diagnosis were available for 194 of these patients. Details of these index cases are given in Table 2. The mean time between onset of symptoms and diagnosis was 13·7 and 16·3 years for males and females, respectively. For some patients there was a delay of > 50 years before correct diagnosis, and delays of > 20 years between onset of symptoms and diagnosis were common (Fig. 1). Many different medical specialists were often involved in the diagnosis, including nephrologists, paediatricians, dermatologists, geneticists, ophthalmologists, cardiologists, neurologists, rheumatologists and general practitioners.

Table 1 Characteristics of the 366 patients with Fabry disease at entry into the Fabry Outcome Survey

	Males	Females
Age at entry (years)	35·5 ± 13·1 (n = 201)	41·4 ± 17·1 (n = 165)*
Age at diagnosis (years)	24·6 ± 13·8 (n = 185)	33·8 ± 16·0 (n = 141)*
Weight at entry (kg)	67·0 ± 16·2 (n = 149)	63·3 ± 13·8 (n = 114)

*$P < 0·001$ compared with males.
Values are means ± SD for the number of patients in parentheses.

Table 2 Characteristics of the 194 index cases of Fabry disease in the Fabry Outcome Survey

	Males (n = 133)	Females (n = 61)
Age at onset of symptoms (years)	10·9 ± 7·1	22·6 ± 16·2
Age at diagnosis (years)	24·6 ± 13·2	38·8 ± 14·8
Time between symptom onset and diagnosis (years)	13·7 ± 12·9	16·3 ± 14·7

Values are means ± SD.

Previous misdiagnoses

The range and relative frequency of previous misdiagnoses are shown in Table 3. 'Other' includes a wide range of diseases and symptoms, including renal disease, irritable bowel syndrome, Raynaud's syndrome, coronary heart disease, and 'growing pains'. Overall, 25% of patients had been previously misdiagnosed.

Enzyme activity and genotype analysis

Activity of α-galactosidase A was measured in 152 males and 119 females. Enzyme activity was decreased in 113, normal in one and undetectable in 38 male patients. In females, enzyme activity was decreased, normal and undetectable in 62, 56 and one patient, respectively.

Genotyping was performed in 44% of patients (49% of males and 37% of females) without and in 77% of patients (75% of males and 78% of females) with an affected family

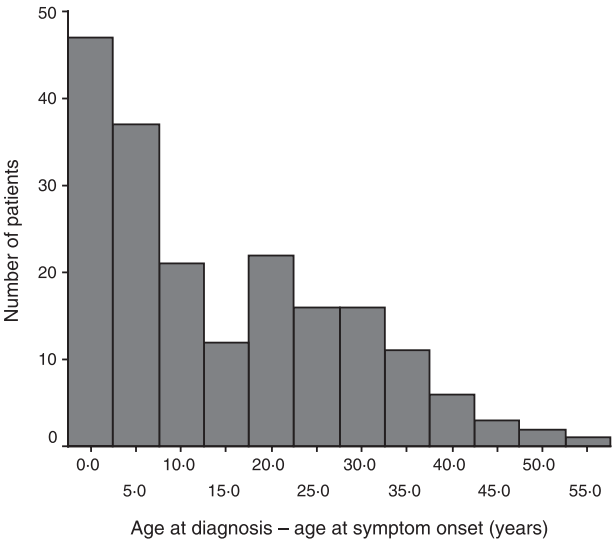

Figure 1 Delay in diagnosis after onset of symptoms in 194 index cases of Fabry disease in the Fabry Outcome Survey.

Table 3 Previous misdiagnoses of patients in the Fabry Outcome Survey

Misdiagnosis	Percentage of misdiagnoses
Rheumatological disease/rheumatic fever	39
Arthritis	15
Fibromyalgia syndrome	7
Dermatomyositis	5
Erythromelalgia	5
Osler's disease	5
Neuropsychological disease	13
Ménière's disease	3
Other	49

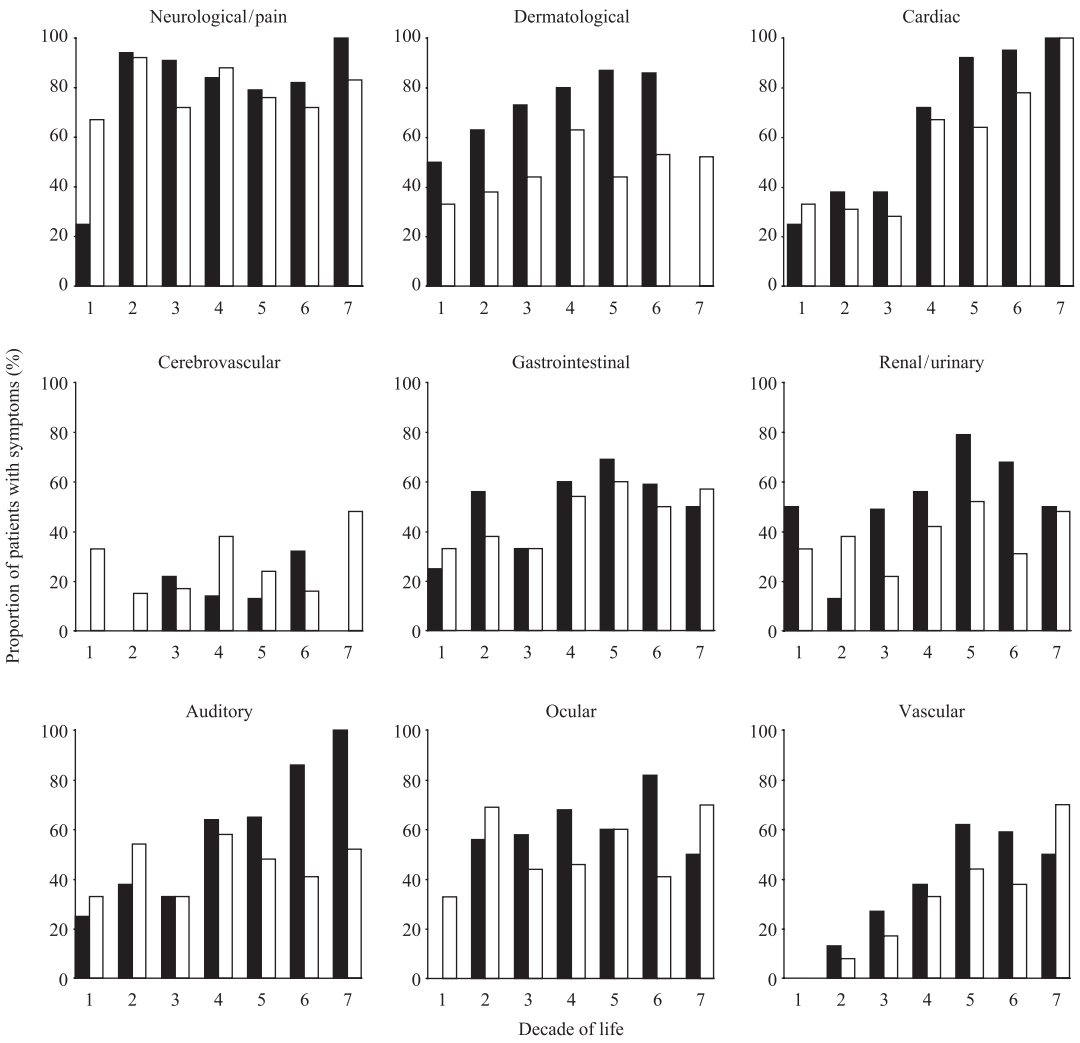

Figure 2 Reported signs and symptoms of Fabry disease according to age at entry into the Fabry Outcome Survey in hemizygous males (■) and heterozygous females (□).

member. Results of genomic and/or enzyme investigations were available within the database for 236 of the 268 (88%) patients where the diagnosis had not been made based on family pedigree. Data were not available for the other 12% of patients.

Reported signs and symptoms in male and female patients

The main signs and symptoms of Fabry disease in male and female patients, according to age at entry into the FOS, are shown in Fig. 2. None of the patients had no signs or symptoms of the disease, and even patients less than 10 years of age had manifestations of Fabry disease in at least one organ system. In the majority of patients, multiple organ systems were involved. In only 23 of the patients studied was there involvement of only a single organ. In these patients the involvement was dermatological ($n = 3$), ocular ($n = 3$), general (allergy; $n = 2$), neurological ($n = 12$) and renal ($n = 3$). Eighteen of these patients were less than 30 years of age and 13 were females. There was no evidence for a specific cardiac or renal variant. Generally, the number of organ systems involved rose progressively with age in both males and females, although the number of systems involved was higher in males. By 50–60 years of age the mean number of organ systems involved was 9·5 (range, 5–13) in males and 6·0 (range, 1–12) in females.

The most frequently reported signs and symptoms of Fabry disease were neurological, and were reported by the majority of both male (84%) and female (79%) patients. The most prevalent of the neurological symptoms was neuropathic pain, which occurred in 76% of males and 64% of females and began at a mean age of 9·4 and 16·9 years, respectively. Dermatological symptoms occurred in 78% of males and 50% of females in FOS, and angiokeratomas were present from a mean age of 17·9 years in males and 29·1 years in females.

Renal signs and symptoms of Fabry disease were reported in 50% of patients in FOS. The most frequently reported sign was proteinuria, which was observed in 44% of males and 33% of females. End-stage renal failure was present in 17% of males (10% with renal transplants and 7% on dialysis) and 1% of females (1 patient on dialysis who was subsequently transplanted) aged > 18 years.

Cardiac symptoms, including angina, arrhythmias and dyspnoea, were reported in 69% of male and 65% of female patients in FOS. Left ventricular hypertrophy (LVH) was observed in 46% of males and 28% of females. The age at onset of LVH in males and females was 38·0 and 55·4 years, respectively.

The frequency of cerebrovascular events [stroke, transient ischaemic attack (TIA), prolonged reversible ischaemic neurologic deficit] was higher in women than in men, with 12% of male and 27% of female patients reporting these incidents. Although the mean age at onset of cerebrovascular events was 28·8 years in males and 43·4 years in females, the youngest patient to report a TIA was a boy aged 12 years. This is the first report of a TIA in a child with Fabry disease. In addition, one female patient reported a TIA at the age of 25 years, and 'other' non-defined cerebrovascular events were reported for five further females aged less than 30 years.

Vascular signs and symptoms were not reported in the first decade of life, but rose progressively thereafter in both males and females. In total, vascular manifestations were recorded in approximately 45% of male patients and 35% of females.

Auditory symptoms, such as tinnitus and hearing loss, were reported in 57% of male and 47% of female patients, and ocular signs in 62% of males and 53% of females. Gastrointestinal symptoms, including abdominal pain and diarrhoea, were reported in 55% of males and 50% of females. Fatigue was reported in 24% of males and 28% of females.

Concomitant medication

A wide range of symptomatic medication is recorded in the FOS database. Approximately 75% of patients are on analgesic medication, approximately 22% on non-steroidal anti-inflammatory drugs, approximately 25% on anticoagulants and 25% on diuretics.

Mortality

Age and cause of death have been reported for 42 male and 24 affected female relatives of patients in FOS. The mean age at death (± SD) was 45·5 ± 12·6 years and 55·4 ± 14·9 years for the male and female relatives, respectively. The primary cause of death in affected male relatives was renal failure, which occurred in 54·5% of cases. Death from renal causes was significantly ($P < 0·001$) more common in males than in females. Conversely, the most frequent cause of death in affected female relatives, occurring in 26·7% of cases, was cardiac disease.

Discussion

The data presented here from this, the largest cohort of patients with Fabry disease, were obtained after clinical assessment of patients by physicians or nurse specialists. Unlike previous much smaller cohort studies, FOS is not a questionnaire survey. It is a database of baseline clinical observations of all patients known to the participating European centres. MacDermot and coworkers, in a study of 98 male patients in the UK [3], and Galanos and colleagues, in a questionnaire study of 29 men and 38 women in Australia [7], showed that the majority of hemizygous males experience multiple disease manifestations. The present analysis of the FOS database demonstrates that females are usually (often severely) affected. Although this has been suggested by recent smaller studies [4,6–8] it is not accepted by all authorities. It is now clear from FOS that females heterozygous for Fabry disease should no longer be considered as asymptomatic 'carriers'. In fact, they may exhibit the full range of disease manifestations, although the signs and symptoms are more variable than those in men, and the disease appears to have a slower rate of progression. Average age of death of affected relatives of patients in FOS was 55 years for women and 45 years for men. This represents a significant reduction in life-expectancy. The present analysis also illustrates the limitations of using enzyme levels to confirm the diagnosis of Fabry disease in women, as α-galactosidase A activity was within the normal range in about half of the symptomatic women in the database. Even in men, the use of artificial substrate to measure α-galactosidase A activity may be misleading, as one of the male patients in FOS had normal enzyme levels but genotypically confirmed Fabry disease.

Phenotypic expression of Fabry disease in heterozygous women can most likely be explained by the Lyon hypothesis, or random X-inactivation [19,20]. This normal physiological phenomenon occurs early in embryonic development and acts to equalize gene dosage effects on the sex chromosomes. At the onset of X-inactivation, one or other of the X-chromosomes is inactivated in each cell of the embryo and remains inactive throughout all further somatic cell divisions. Females heterozygous for X-linked diseases are therefore mosaics, with different cells in the body expressing either the normal or disease gene [20]. This accounts for the variability of both symptoms and circulating levels of α-galactosidase A in female heterozygotes. Skewed X-inactivation may also occur [21]. The dramatic influence of skewed X-inactivation has been demonstrated by a set of female monozygotic twins with a mutation in the α-galactosidase A gene [22]. Analysis of the twins' fibroblasts revealed that one of the twins had a preferentially active maternally derived X-chromosome and was asymptomatic. The other twin had a Fabry disease phenotype and a preferentially active paternally derived X-chromosome, indicating that the mutation was on the paternal X-chromosome and that differences in X-inactivation were responsible for the symptomatology. The frequent occurrence of clinical disease in female heterozygotes also indicates a lack of enzymatic complementation.

Although Fabry disease is a progressive condition with life-threatening renal, cardiac and cerebrovascular manifestations developing generally during the third and fourth decade of life, the present analysis shows that many symptoms of the disease occur before 10 years of age. Neurological pain, gastrointestinal symptoms, angiokeratoma and corneal dystrophy (cornea verticillata) are particularly common in childhood and their unexplained presence should alert the physician to the possibility of Fabry disease, as should proteinuria of unknown aetiology.

Analysis of the index cases in FOS illustrates the problem of misdiagnosis of Fabry disease, particularly where there is no existing case within a family. The mean time between onset of symptoms and correct diagnosis in these patients was 14·5 years for males and 16·8 years for females. Similar delays in diagnosis have been reported in the Australian cohort (≥ 10 years in nearly all index cases) [7] and in the UK study [3]. In the latter study, diagnosis was made at a mean of 8 and 10 years after the development of neuropathic pain and angiokeratoma, respectively, in males [3]. This delay in diagnosis, together with the range of different specialists (e.g. nephrologists, dermatologists, cardiologists, ophthalmologists), as well as general practitioners, who may encounter the signs and symptoms of Fabry disease, emphasizes the importance of raising awareness of the disease phenotype among healthcare workers. This is now particularly important because ERT is available [9].

Interestingly, there was no evidence in the FOS cohort of a milder late-onset atypical variant of Fabry disease with manifestations limited to the heart [14–16], kidney [17] or the heart and kidney [18]. The possibility of a cardiac variant of Fabry disease has attracted particular attention recently. In a study of 153 consecutively referred male patients to a national referral centre for hypertrophic cardiomyopathy in the UK, six individuals were found to have Fabry disease. Retrospective clinical evaluation revealed other symptoms of Fabry disease in only one of these six patients [16]. If a cardiac variant does exist, then it is clear that Fabry disease is not as rare as suggested previously in the literature.

In conclusion, despite the ascertainment bias that may be present in FOS (less severely affected patients are less likely to be diagnosed and therefore included in the database), this survey has provided a detailed cross-sectional description of the natural history of Fabry disease in a large cohort of patients. Significant clinical symptoms have been demonstrated in heterozygous females, and it is now clear that they should be considered as patients rather than carriers of Fabry disease. It is also apparent that signs and symptoms of the disease occur at an early age in children. The present analysis of baseline data will provide a benchmark against which the therapeutic effects of ERT can be measured.

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