Time delays in the diagnosis and treatment of Fabry disease

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Disclosures

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ABSTRACT

Background: The high variability in clinical manifestations of Fabry disease can lead to delays between symptom onset and correct diagnosis, and between correct diagnosis and initiation of enzyme replacement therapy. We investigated whether these delays have improved in recent years.

Methods: Data were analyzed from the Fabry Outcome Survey (FOS; Shire; extracted August 2013) for “index patients”, defined as the first patient diagnosed with Fabry disease from a family with several or no additional members registered in FOS.

Results: Periods analyzed: 2001–2006 versus 2007–2013, in patients overall and from Europe versus the rest of the world (ROW). Overall, 598 patients were diagnosed within the study periods. Median age (95% CI) at symptom onset in 2001–2006 and 2007–2013 was 7.0 (5.0–11.0) and 9.0 (6.0–11.0) in children, and 21.0 (15.0–28.0) and 31.0 (26.0–35.0) in adults, respectively. Overall, the delay in diagnosis did not improve, despite showing a trend towards earlier diagnosis in adults (median 14.0 [95% CI 9.0–20.0] vs. 10.5 [8.0–13.0] years) and children (5.0 [1.0–9.0] vs. 4.0 [0.0–8.0] years). In contrast, the delay in treatment onset significantly decreased from 2001–2006 to 2007–2013 in children (4.3 [2.0–7.0] vs. 1.0 [0.8–1.4] year; $p < 0.001$) and adults (2.1 [1.3–3.2] vs. 0.9 [0.8–1.1] years; $p < 0.001$). Geographically, the delay in treatment onset significantly decreased in the ROW among children (5.3 [4.2–8.0] vs. 1.0 [0.8–1.4] year; $p < 0.001$) and adults (5.4 [4.8–6.0] vs. 1.1 [0.9–1.1] year; $p < 0.001$), but it did not change in Europe.

Conclusion: We found that the delay in diagnosis has not improved substantially whereas the delay in treatment onset has improved in recent years.

What is already known about this topic?

The heterogeneous nature and severity of Fabry disease symptoms, plus wide variations in the age at which they manifest, can hinder a correct diagnosis of this disease, delaying treatment initiation. Enzyme replacement therapy is considered most beneficial when started early in the disease course; therefore, it is essential that awareness and knowledge of Fabry disease be spread amongst the medical community to shorten the time to diagnosis.

What does this article add?

We investigate whether knowledge regarding diagnosis and treatment of Fabry disease has improved in recent years. By analyzing data from index patients included in the Fabry Outcome Survey, we found that the delay in treatment onset has significantly improved, although the delay in diagnosis has not. Our geographical analysis shows a significant decrease in treatment delay for patients outside of Europe compared with those within, and we also show how numbers diagnosed by different medical specialties has changed in recent years.

Introduction

Fabry disease is an X-linked lysosomal storage disorder caused by a functional deficiency of alpha-galactosidase A. Deficiency of this enzyme results in progressive accumulation of glycosphingolipids, particularly globotriaosylceramide (Gb_3), in many different cell types throughout the body [1]. Clinical manifestations of classical Fabry disease typically begin in adolescence, including acroparesthesia and abdominal pain [2], and progress over the disease course, resulting in premature death from renal, cardiovascular, or cerebrovascular complications, often around the fifth decade of life in men [3] and seventh in women [4]. Until recently, Fabry disease in women was thought to be largely asymptomatic [1], but closer observations have revealed that women may experience the same signs and symptoms as men, although typically with a higher degree of variability and occurring later in life [5, 6].

Enzyme replacement therapy (ERT) has been shown to stabilize and improve many of the signs and symptoms of Fabry disease [7-12]. Starting treatment early in the disease course may halt the progression towards irreversible organ damage and the subsequent development of associated life-threatening complications. Unfortunately, the diagnosis of Fabry disease is confounded by high variability in terms of organ system involvement, age at onset, and severity of Fabry disease clinical features, often resulting in misdiagnosis or delayed diagnosis [13]. Patients may seek help from multiple medical specialists before a correct diagnosis is made, resulting in delayed treatment initiation.

A study of FOS data soon after ERT for Fabry disease became available in 2001, identified mean delays from symptom onset to correct Fabry disease diagnosis of 13.7 years in males and 16.3 years in females [6]. Subsequent research showed only a slight improvement in mean delay (12.2 years in males and 12.4 years in

females) [14], indicating that provision of treatment early in the course of Fabry disease remained unlikely for many patients.

Since the publication of earlier works analyzing the delay in Fabry disease diagnosis, several active educational projects have been conducted to spread the knowledge about this condition and to make the different specialists who could potentially encounter Fabry disease cases more familiar with it. Whether patients with Fabry disease are now being diagnosed sooner and started on treatment earlier in the disease course is unknown.

The objective of this study was to evaluate whether delays in Fabry disease diagnosis and treatment have improved in recent years.

Materials and methods

Patients and study design

Patient data were extracted from the Fabry Outcome Survey (FOS), an international registry initiated in 2001 (sponsor: Shire) for the collection of long-term data to help increase the understanding of the natural history of Fabry disease. The data extraction date for this study was August 2013. Patients diagnosed with Fabry disease who are untreated or receiving treatment with agalsidase alfa are eligible for inclusion in FOS. The Ethics Committees/Institutional Review Boards of all participating centers have approved conduct of the FOS registry. All patients, or their caregivers or legal guardians in the case of children, provide written informed consent/assent before data can be entered into the FOS database, and the data are anonymized prior to analysis.

The current study focuses on FOS index patients. “Index patient” was previously defined as a patient with Fabry disease who was not diagnosed as a

result of having an affected family member [6]. This study includes the first patient with a diagnosis of Fabry disease from a family with several members or no additional members registered in FOS. Patients were excluded if they had a negative delay in diagnosis (i.e. if they were diagnosed before symptom onset). Children are defined as patients who were younger than 18 years of age at diagnosis.

Data analysis

Enzyme replacement therapy with agalsidase alfa became available in 2001. For the analyses herein, index patients registered in FOS from 2001 up to date (2013) were identified and divided into groups according to their year of diagnosis. The groupings of 2001–2006 and 2007–2013 were chosen so that a similar time period was covered by each group. To investigate whether the delay in Fabry disease diagnosis has decreased in recent years, the time between first symptoms and diagnosis in all patients (treated plus untreated) diagnosed between 2007 and 2013 was compared with that in patients diagnosed between 2001 and 2006. To investigate whether the delay between diagnosis and treatment onset has decreased since 2001, the time between Fabry disease diagnosis and treatment onset in patients diagnosed during 2007–2013 was compared with that in treated patients diagnosed during 2001–2006.

Delays in diagnosis and treatment onset were also evaluated for the geographical regions in which agalsidase alfa is approved for commercial use, designated herein as Europe and the rest of the world (ROW).

The severity of disease manifestations reported for adult patients diagnosed during 2001–2006 and 2007–2013 was assessed using the FOS-Mainz Severity Score Index (FOS-MSSI) obtained at treatment onset. The type of specialist who first suspected Fabry disease was also analyzed in patients diagnosed before 2006 (thus

including patients who were diagnosed before the FOS registry was initiated and who were subsequently entered into the database) and during 2007–2013.

Statistical analyses

Descriptive statistics were calculated and differences were assessed using Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. The analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

At the time of data extraction, 598 patients had been diagnosed within the study periods (Figure 1) and are included herein. This study focuses on the delay in diagnosis and treatment onset; however, age at diagnosis, symptom onset, and ERT initiation is provided for reference in the Supporting Information Table S1.

Delay in diagnosis

A trend towards early diagnosis was noted for both children and adults, although none of the differences were statistically significant (Table 1). Moreover, many patients continue to experience delays in Fabry disease diagnosis of 30 years and more (Figure 2).

Of a total of 598 index patients enrolled in FOS and included in our study, 267 (44.6%) were from Europe and 331 (55.4%) were from the ROW. For children, no statistically significant differences were found in the delay in diagnosis during 2007–2013 compared with 2001–2006 in either region (Table 2). Considering only adults,

we identified a shorter delay in diagnosis during the more recent period only in Europe (p = 0.048; Table 2).

Delay in treatment onset

The delay between Fabry disease diagnosis and treatment onset was statistically significantly shorter in children diagnosed during 2007–2013 (median 1.0 [95% CI 0.8–1.4] year) than during 2001–2006 (4.3 [95% CI 2.0–7.0] years; p < 0.001; Table 1). This delay in treatment onset was also statistically significantly shorter in adults diagnosed during 2007–2013 (0.9 [95% CI 0.8–1.1] years) than during 2001–2006 (2.1 [95% CI 1.3-3.2] years; p < 0.001; Table 1).

Geographical analysis

The delay between Fabry disease diagnosis and treatment onset was shorter for children and adults in Europe than in the ROW during 2001–2006, but was quite similar during 2007–2013. No statistically significant change was found for either children or adults in Europe diagnosed during 2007–2013 when compared with those diagnosed during 2001–2006 (Table 2). However, a statistically significant decrease in the delay between Fabry disease diagnosis and treatment onset was found for both children and adults in the ROW. For children, the median delay shows a decrease from 5.3 (95% CI 4.2–8.0) years in those diagnosed during 2001–2006 to 1.0 (95% CI 0.8–1.4) years in those diagnosed during 2007–2013 (p < 0.001; Table 2). For adults, the median delay decreased from 5.4 (95% CI 4.8–6.0) years in those diagnosed during 2001–2006 to 1.1 (95% CI 0.9–1.1) years in those diagnosed during 2007–2013 (p < 0.001; Table 2).

Disease expression and diagnosis by medical specialists

Overall, adult FOS MSSI scores at treatment initiation did not differ between patients from each period. The FOS-MSSI scores at treatment initiation were lower in adult females than adult males during both 2007–2013 ($p = 0.003$) and 2001–2006 ($p = 0.016$; Table 3).

The aggregate proportion of index patients diagnosed by geneticists, general practitioners, pediatricians, and internists significantly increased in recent years (18.9% before 2006 vs. 39.6% in 2007–2013; $p < 0.001$) compared with no change in the aggregate proportion diagnosed by cardiologists, nephrologists, and neurologists (41.1% before 2006 vs. 41.6% in 2007–2013; Table 4).

Discussion

Delay in diagnosis

The current study shows that, overall, the delay in Fabry disease diagnosis has shown a non-significant trend towards improvement in recent years. It also shows that ERT now seems to be initiated sooner after diagnosis than when it first became available. We found a similar mean delay in Fabry disease diagnosis in adults in recent years to that of the 13.7 years for males and 16.3 years for females described by Mehta et al in 2004 [6], and also the 12.2 years for males and 12.4 years for females reported by Beck in 2006 [14]. Moreover, the Fabry Registry reported an even larger gap between median age at symptom onset and diagnosis of 14 years for males and 19 years for females [15]. In agreement with findings from Mehta et al [6], we also found that some patients still experienced delays in excess of 30 years before a correct diagnosis was made (Figure 1). The reduction in median delay in diagnosis of 9.5 years in adult males is very encouraging but still insufficient, and

shows that further efforts to reduce the delay in Fabry disease diagnosis are needed to improve patient care. The prompt diagnosis of index patients is also likely to result in earlier diagnosis of affected relatives and could have a strong impact on the management of a significant number of patients. A median of five Fabry disease carriers are diagnosed from each index patient identified [16]; therefore, the "cumulative impact" of prompt diagnosis within a family is not negligible.

Patients with cardiac and renal Fabry disease variants may present with later-onset left ventricular hypertrophy [17] or end-stage renal disease [18] without previous classical manifestations. The prevalence of these Fabry disease variants may be greater than originally thought [17, 18], and may help explain the delay in diagnosis experienced by some patients. Unfortunately, on this occasion, we were not able to confirm the number of patients with cardiac and renal variants of Fabry disease due to mutation data being unavailable. A previous analysis of FOS data, however, found no evidence of late-onset cardiac or renal variants with milder disease [6], although the definitions used to identify these Fabry disease variants were not provided.

Delay in treatment onset

Whilst other studies have investigated the delay between symptom onset and diagnosis in Fabry disease with reference to timely treatment strategies [6, 14], the delay between diagnosis and treatment onset has not been well investigated. In this study, the significant reduction in the delay between diagnosis and ERT initiation that was observed after 2007 is of utmost importance. The most likely reason for why we still have an important delay in recognizing Fabry disease patients is that during the diagnosis process physicians of many different specialties are involved and their

awareness of this rare disorder is still limited. Nevertheless, once new Fabry disease patients have been identified, treatment could possibly be started earlier due to their referral to centers of great experience and thus awareness that early treatment is an essential goal for improving or stabilizing Fabry disease symptoms [19, 20].

Geographical analysis

The improvement in delay in diagnosis in recent years for adults in Europe, and particularly the significant improvement in treatment delay in the ROW, may reflect wider education of Fabry disease and its signs and symptoms and improved availability of agalsidase alfa ERT in the ROW. The regional differences found in this study are relevant and a specific analysis of educational programs undertaken in Europe versus those performed in the ROW could shed light on which programs would be best carried out moving forward, now that ERT is widely available.

Disease expression and diagnosis by medical specialists

This study shows that adult patients diagnosed after 2007 had a similar level of disease severity as those diagnosed in 2001–2006. Improvements in the recognition of late-onset variants and less severe forms of Fabry disease in females could be expected to result in more patients with milder disease being diagnosed. In the current analysis, breakdown by gender revealed that neither males nor females differed significantly in disease severity between the diagnosis periods.

The aggregate proportion of patients diagnosed with Fabry disease by geneticists, general practitioners, pediatricians, and internists appears to be approaching that diagnosed by cardiologists, nephrologists, and neurologists, which may reflect increasing awareness of this multi-systemic disorder throughout the

wider medical community. This may explain the earlier diagnosis identified in some regions of the world, such as Europe. Geneticists were the leading specialists in diagnosing index patients with Fabry disease during 2007–2013. While a proportion of these index patients would have been diagnosed by geneticists through family screening, it is also recognized that many are likely to have been referred by other specialists who suspected Fabry disease, thus geneticists would have confirmed the final diagnosis.

This study was subject to several limitations. FOS is a registry for real-world data collection and was not specifically designed to collect data on all of the parameters reported in this retrospective study. Furthermore, there is the possibility that data in FOS are subject to ascertainment bias, whereby patients with less severe Fabry disease may not have been diagnosed and therefore were not included. Also, age at symptom onset may be subject to recall bias. Though the FOS registry contains one of the largest datasets on Fabry disease, the sample sizes in our analysis remain small, especially for children, which may have prevented a statistically significant improvement in the delay in diagnosis from being reached. However, small samples sizes are to be expected in the rare disease arena.

Despite efforts to increase education and awareness of Fabry disease in recent years, early recognition is still a challenge and an unmet need. There is still the necessity for pediatricians and pediatric rheumatologists to recognize when pain is neuropathic and not due to bone or joint origins. We need to increase awareness that angiokeratomas and cornea verticillata, as observed in routine controls, are frequent and early signs in Fabry disease. Earlier diagnosis may also be helped by ear, nose and throat specialists including Fabry disease among the differential diagnoses of sudden hearing loss. Since access to online health information has

rapidly increased in recent years, websites dedicated to raising awareness of Fabry disease signs and symptoms in the general population could be an important tool. All of these factors will help increase the likelihood of Fabry disease being suspected before cardiac, renal, or cerebrovascular complications occur.

Conclusions

Our analysis shows that the delay in diagnosis has decreased, but not significantly, while the delay in treatment onset has shown a statistically significant improvement. Geographical differences have an impact on both parameters and the causes of regional differences should be investigated further to gather evidence on this neglected aspect of Fabry disease management. Further studies are required to confirm the results found herein and to monitor the status of diagnosis and treatment delays in Fabry disease.

Author contributions

Ricardo Resin and Pablo García-Pavía designed the study, Amandine Perrin performed the statistical analysis and all authors interpreted the data. All authors contributed to the first draft, critically reviewed and revised subsequent drafts, and approved the final draft.

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Table 1 Delay in years between onset of symptoms and diagnosis and between diagnosis and onset of treatment of index patients, by year of diagnosis (*n* = 598 index patients with available diagnosis date and diagnosed during or after 2001; *n* = 467 of these were treated with ERT and included in the analysis of delay between diagnosis and treatment onset)

Characteristic	Diagnosis period	Statistics	Girls (*n* = 26)	Boys (*n* = 55)	Total children (*n* = 81)	Adult females (*n* = 256)	Adult males (*n* = 261)	Total adults (*n* = 517)
Delay between symptom onset and diagnosis (years)	2001–2006	*n* (missing)	5 (7)	16 (7)	21 (14)	64 (43)	67 (21)	131 (64)
		Mean (SD)	4.0 (4.3)	6.0 (5.2)	5.5 (5.0)	16.4 (16.5)	17.0 (13.8)	16.7 (15.1)
		Median (95% CI)	3.0 (0.0–9.0)	5.0 (1.0–11.0)	5.0 (1.0–9.0)	12.0 (7.0–19.0)	19.0 (9.0–22.0)	14.0 (9.0–20.0)
	2007–2013	*n* (missing)	3 (11)	20 (12)	23 (23)	82 (67)	112 (61)	194 (128)
		Mean (SD)	1.3 (2.3)	4.9 (4.1)	4.4 (4.1)	15.1 (15.4)	14.7 (14.9)	14.9 (15.1)
		Median (95% CI)	0.0 (0.0–4.0)	4.0 (1.0–8.0)	4.0 (0.0–8.0)	11.0 (5.0–17.0)	9.5 (6.0–13.0)	10.5 (8.0–13.0)
		Wilcoxon p-value	NS	NS	NS	NS	NS	NS
			Girls (*n* = 14)	Boys (*n* = 45)	Total children (*n* = 59)	Adult females (*n* = 184)	Adult males (*n* = 224)	Total adults (*n* = 408)
Delay between diagnosis and treatment onset (years)	2001–2006	*n* (missing)	8 (0)	18 (0)	26 (0)	72 (0)	81 (0)	153 (0)
		Mean (SD)	4.5 (3.6)	4.4 (3.1)	4.4 (3.2)	3.3 (2.8)	3.1 (3.0)	3.2 (2.9)
		Median (95% CI)	3.4 (0.8–9.5)	4.4 (1.0–7.0)	4.3 (2.0–7.0)	2.8 (1.3–3.7)	1.8 (0.9–3.4)	2.1 (1.3–3.2)
	2007–2013	*n* (missing)	6 (0)	27 (0)	33 (0)	112 (0)	143 (0)	255 (0)
		Mean (SD)	1.6 (1.1)	1.2 (0.7)	1.3 (0.8)	1.4 (1.1)	1.1 (0.9)	1.2 (1.0)
		Median (95% CI)	1.3 (0.7–3.6)	1.0 (0.7-1.4)	1.0 (0.8–1.4)	1.0 (0.9–1.2)	0.8 (0.7–1.0)	0.9 (0.8–1.1)
		Wilcoxon p-value	NS	0.002	<0.001	<0.001	<0.001	<0.001

CI, confidence interval; SD, standard deviation.
(Missing) indicates the number of patients missing the dates of symptom and treatment onset.

Table 2 Delay in years between onset of symptoms and diagnosis and between diagnosis and onset of treatment of index patients, by region and year of diagnosis (of the *n* = 598 patients with an available diagnosis date during or after 2001, *n* = 267 were from Europe and *n* = 331 were from the ROW; *n* = 467 were treated with ERT and included in the analysis of delay between diagnosis and treatment onset)

			Europe						ROW					
Characteristic	**Diagnosis period**	**Statistics**	**Girls (*n* = 15)**	**Boys (*n* = 23)**	**Total children (*n* = 38)**	**Adult females (*n* = 122)**	**Adult males (*n* = 107)**	**Total adults (*n* = 229)**	**Girls (*n* = 11)**	**Boys (*n* = 32)**	**Total children (n = 43)**	**Adult females (*n* = 134)**	**Adult males (*n* = 154)**	**Total adults (*n* = 288)**
Delay between symptom onset and diagnosis (years)	2001–2006	*n* (missing)	4 (3)	8 (2)	12 (5)	39 (23)	38 (8)	74 (31)	1 (4)	8 (5)	9 (9)	25 (20)	32 (13)	57 (33)
		Mean (SD)	5.0 (4.2)	8.6 (5.0)	7.4 (4.9)	15.8 (16.1)	20.6 (14.4)	18.0 (15.4)	–	3.3 (4.1)	2.9 (4.0)	17.4 (17.4)	13.0 (12.0)	15.0 (14.6)
		Median (95% CI)	5.5 (0.0–9.0)	8.5 (5.0–15.0)	8.0 (3.0–11.0)	12.0 (5.0–20.0)	21.0 (14.0–27.0)	16.0 (12.0–21.0)	–	1.5 (0.0–12.0)	1.0 (0.0–5.0)	12.0 (3.0–26.0)	9.0 (3.0–22.0)	10.0 (6.0–20.0)
	2007–2013	*n* (missing)	1 (7)	8 (5)	9 (12)	30 (30)	35 (29)	65 (59)	2 (4)	12 (7)	14 (11)	52 (37)	77 (32)	129 (69)
		Mean (SD)	–	6.9 (3.9)	6.1 (4.3)	9.8 (12.1)	16.3 (15.7)	13.3 (14.4)	2.0 (2.8)	3.5 (3.8)	3.3 (3.6)	18.2 (16.4)	14.0 (14.6)	15.7 (15.4)
		Median (95% CI)	–	7.5 (3.0–12.0)	7.0 (1.0–11.0)	5.5 (0.6–11.0)	12.0 (6.0–18.0)	9.0 (5.0–13.0)	2.0 (0.0–4.0)	2.5 (0.0–8.0)	2.5 (0.0–8.0)	16.0 (9.0–22.0)	8.0 (5.0–13.0)	11.0 (8.0–17.0)
		Wilcoxon p-value	NS	NS	NS	NS	NS	0.048	NS	NS	NS	NS	NS	NS

			Europe						ROW					
Characteristic	**Diagnosis period**	**Statistics**	**Girls (*n* = 7)**	**Boys (*n* = 17)**	**Total children (*n* = 24)**	**Adult females (*n* = 84)**	**Adult males (*n* = 89)**	**Total adults (*n* = 173)**	**Girls (*n* = 7)**	**Boys (*n* = 28)**	**Total children (n = 35)**	**Adult females (*n* = 100)**	**Adult males (*n* = 135)**	**Total adults (*n* = 235)**
Delay between diagnosis and treatment onset (years)	2001–2006	*n* (missing)	6 (0)	8 (0)	14 (0)	43 (0)	41 (0)	84 (0)	2 (0)	10 (0)	12 (0)	29 (0)	40 (0)	69 (21)
		Mean (SD)	3.3 (3.3)	2.8 (3.8)	3.0 (3.5)	2.3 (2.7)	1.3 (1.7)	1.8 (2.3)	8.0 (0.1)	5.6 (1.7)	6.0 (1.8)	4.8 (2.3)	5.0 (2.7)	4.9 (2.5)
		Median (95% CI)	2.2 (0.6–9.5)	0.8 (0.1–8.8)	1.5 (0.7–8.7)	1.2 (0.8–2.5)	0.7 (0.5–1.0)	0.9 (0.7–1.2)	8.0 (7.9–8.1)	5.2 (4.2–8.0)	5.3 (4.2–8.0)	4.9 (3.4–6.0)	5.6 (4.9–6.4)	5.4 (4.8–6.0)
	2007–2013	*n* (missing)	1 (0)	9 (0)	10 (0)	41 (0)	48 (0)	89 (0)	5 (0)	18 (0)	23 (0)	71 (0)	95 (0)	166 (32)
		Mean (SD)	–	1.3 (0.9)	1.2 (0.9)	1.1 (1.0)	0.9 (0.8)	1.0 (0.9)	1.8 (1.1)	1.1 (0.7)	1.3 (0.8)	1.5 (1.1)	1.2 (0.9)	1.3 (1.0)
		Median (95% CI)	–	1.2 (0.2–2.4)	1.1 (0.2–2.4)	0.8 (0.7–1.2)	0.6 (0.5–0.8)	0.7 (0.6–0.9)	1.6 (0.8–3.6)	0.9 (0.6–1.4)	1.0 (0.8–1.4)	1.1 (1.0–1.4)	1.0 (0.8–1.1)	1.1 (0.9–1.1)
		Wilcoxon p-value	NS	NS	NS	NS	NS	NS	NS	<0.001	<0.001	<0.001	<0.001	<0.001

CI, confidence interval; NS, not significant; SD, standard deviation.
(Missing) indicates the number of patients missing the dates of symptom and treatment onset.

Table 3 FOS-MSSI at treatment onset of adult patients by year of diagnosis (*n* = 467 treated index patients with an available diagnosis date – 408 adults)

Characteristic	Diagnosis period	Statistics	Adult females (*n* = 184)	Adult males (*n* = 224)	Total adults (*n* = 408)
FOS-MSSI*	2001–2006	*n* (missing)	67 (5)	78 (3)	145 (8)
		Mean (SD)	14.1 (9.6)	18.4 (10.9)	16.4 (10.5)
		Median (95% CI)	11.5† (9.5–15.0)	17.8† (14.5–20.5)	15.0 (12.0–18.0)
	2007–2013	*n* (missing)	111 (1)	134 (9)	245 (10)
		Mean (SD)	12.1 (7.7)	16.1 (10.1)	14.3 (9.3)
		Median (95% CI)	10.0‡ (9.0–13.0)	15.0‡ (11.0–16.0)	12.0 (10.0–15.0)
		Wilcoxon p-value	NS	NS	NS

CI, confidence interval; FOS-MSSI, FOS-Mainz Severity Score Index; NS, not significant; SD, standard deviation.
*Total MSSI scores <20 indicate mild affliction; 20–40 moderate; >40 severe affliction [21].
†2001–2006, adult females versus males: p = 0.016.
‡2007–2013, adult females versus males: p = 0.003.
(Missing) indicates the number of patients missing MSSI scores

Table 4 Type of specialist who suspected Fabry disease in the index patients (*n* = 864 patients had an available diagnosis date, *n* = 496 before 2006 and *n* = 368 during 2007–2013)

Type of specialist FD first suspected by	**All patients**		
	Year of diagnosis		
	Before 2006	**2007–2013**	**Overall[*] *n***
	***n* (%)**	***n* (%)**	**(%)**
Overall	270	202	472
Nephrologist	59 (21.9)	26 (12.9)	85 (18.0)
Cardiologist	32 (11.9)	43 (21.3)	75 (15.9)
Ophthalmologist	44 (16.3)	19 (9.4)	63 (13.4)
Geneticist	8 (3.0)	45 (22.3)	53 (11.2)
Dermatologist	39 (14.4)	6 (3.0)	45 (9.5)
Neurologist	20 (7.4)	15 (7.4)	35 (7.4)
Other	22 (8.2)	9 (4.5)	31 (6.6)
General practitioner	16 (5.9)	13 (6.4)	29 (6.1)
Pediatrician	22 (8.2)	6 (3.0)	28 (5.9)
Internist	5 (1.9)	16 (7.9)	21 (4.5)
Rheumatologist	2 (0.7)	3 (1.5)	5 (1.1)
Gastroenterologist	1 (0.4)	1 (0.5)	2 (0.4)

FD, Fabry disease.
[*]Only index patients with this data available included (49.9%).

Figure legend

Figure 1 Cohort flow diagram

Figure 2 Delay between symptom onset and diagnosis in index patients (*n* = 598 index patients with available diagnosis date and diagnosed after 2001; *n* = 230 diagnosed during 2001–2006 and *n* = 368 diagnosed during 2007–2013)

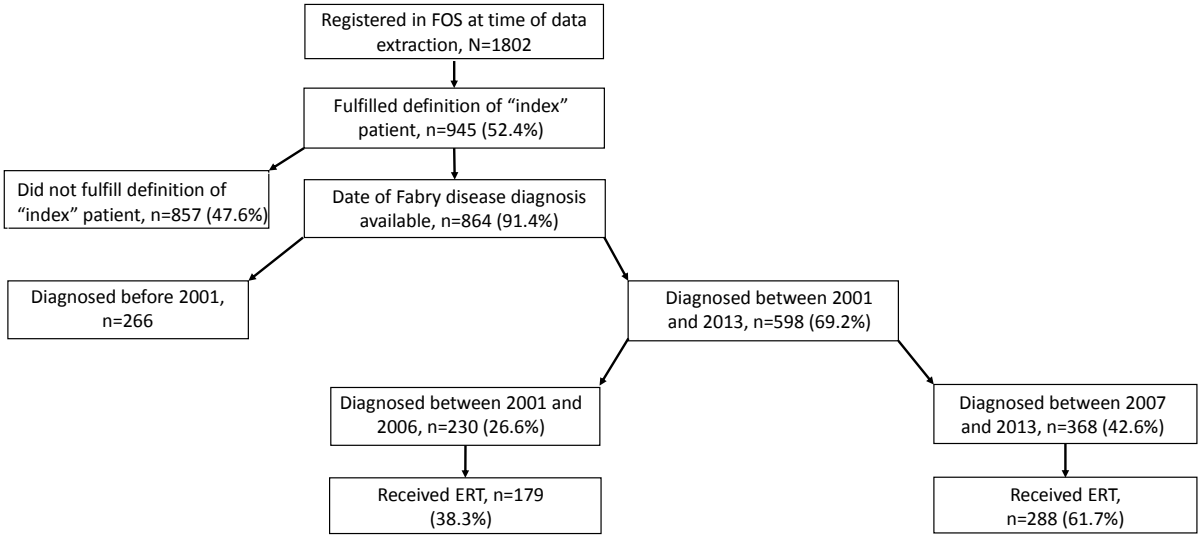
Registered in FOS at time of data extraction, N=1802
Fulfilled definition of "index" patient, n=945 (52.4%)
Did not fulfill definition of "index" patient, n=857 (47.6%)
Date of Fabry disease diagnosis available, n=864 (91.4%)
Diagnosed before 2001, n=266
Diagnosed between 2001 and 2013, n=598 (69.2%)
Diagnosed between 2001 and 2006, n=230 (26.6%)
Diagnosed between 2007 and 2013, n=368 (42.6%)
Received ERT, n=179 (38.3%)
Received ERT, n=288 (61.7%)

Fig 1.

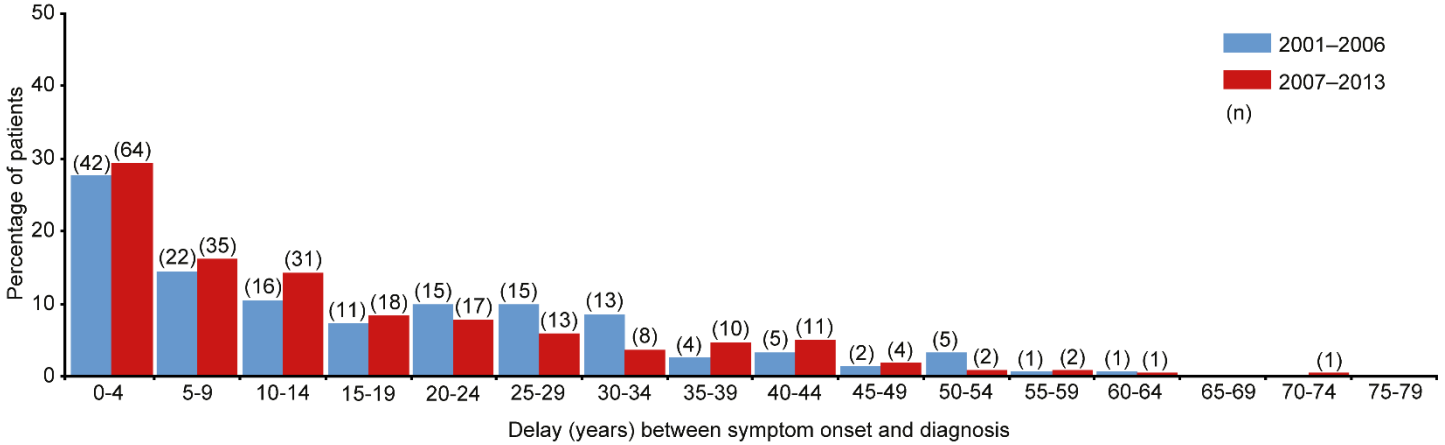
50
40
30
20
10
0
Percentage of patients
2001–2006
2007–2013
(n)
(42) (64)
(22) (35)
(16) (31)
(11) (18)
(15) (17)
(15) (13)
(13) (8)
(4) (10)
(5) (11)
(2) (4)
(5) (2)
(1) (2)
(1) (1)
(1)
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
Delay (years) between symptom onset and diagnosis

Fig 2.

Supporting Information

Table S1 Age at diagnosis, symptom onset, and ERT initiation overall and by year of diagnosis (*n* = 598 index patients with available diagnosis date and diagnosed during or after 2001)

Characteristic	Diagnosis period	Statistics	Girls (n = 26)	Boys (n = 55)	Total children (*n* = 81)	Adult females (*n* = 256)	Adult males (*n* = 261)	Total adults (*n* = 517)
Age at diagnosis (years)	Overall	*n* (missing)	26 (0)	55 (0)	81 (0)	256 (0)	261 (0)	517 (0)
		Mean (SD)	13.1 (3.6)	12.7 (3.3)	12.8 (3.4)	45.3 (13.2)	44.6 (14.7)	44.9 (14.0)
		Median (95% CI)	14.0 (12.0–15.0)	13.0 (12.0–14.0)	13.0 (12.0–14.0)	46.0 (43.0–48.0)	45.0 (40.0–49.0)	45.0 (43.0–48.0)
	2001–2006	*n* (missing)	12 (0)	23 (0)	35 (0)	107 (0)	88 (0)	195 (0)
		Mean (SD)	11.8 (4.2)	13.0 (2.7)	12.6 (3.3)	44.4 (12.3)	40.3 (14.9)	42.54 (13.7)
		Median (95% CI)	13.5 (8.0–15.0)	12.0 (11.0–15.0)	13.0 (12.0–15.0)	45.0 (42.0–49.0)	38.0 (33.0–46.0)	43.0 (39.0–47.0)
	2007–2013	*n* (missing)	14 (0)	32 (0)	46 (0)	149 (0)	173 (0)	322 (0)
		Mean (SD)	14.1 (2.7)	12.4 (3.7)	12.9 (3.5)	45.9 (13.8)	46.7 (14.2)	46.4 (14.0)
		Median (95% CI)	15.0 (12.0–17.0)	13.0 (11.0–14.0)	13.5 (12.0–15.0)	46.0 (43.0–50.0)	47.0 (43.0–51.0)	47.0 (45.0–49.0)
		Wilcoxon p-value	NS	NS	NS	NS	<0.001	0.003
Age at symptom onset (years)	Overall	*n* (missing)	8 (18)	36 (19)	44 (37)	146 (110)	179 (82)	325 (192)
		Mean (SD)	10.6 (3.9)	7.9 (3.7)	8.43 (3.8)	29.8 (17.5)	28.7 (19.6)	29.2 (18.7)

Characteristic	Diagnosis period	Statistics	Girls (n = 26)	Boys (n = 55)	Total children (*n* = 81)	Adult females (*n* = 256)	Adult males (*n* = 261)	Total adults (*n* = 517)
		Median (95% CI)	11.5 (6.0–15.0)	8.5 (6.0–10.0)	9.0 (6.0–10.0)	30.0 (22.0–34.0)	25.0 (20.0–32.0)	26.0 (22.0–31.0)
	2001–2006	*n* (missing)	5 (7)	16 (7)	21 (14)	64 (43)	67 (21)	131 (64)
		Mean (SD)	10.2 (4.9)	7.1 (3.5)	7.9 (4.0)	27.3 (17.1)	24.3 (19.7)	25.8 (18.5)
		Median (95% CI)	12.0 (4.0–15.0)	7.0 (5.0–11.0)	7.0 (5.0–11.0)	25.0 (20.0–34.0)	15.0 (12.0–25.0)	21.0 (15.0–28.0)
	2007–2013	*n* (missing)	3 (11)	20 (12)	23 (23)	82 (67)	112 (61)	194 (128)
		Mean (SD)	11.3 (1.5)	8.6 (3.8)	9.0 (3.7)	31.8 (17.7)	31.3 (19.2)	31.5 (18.5)
		Median (95% CI)	11.0 (10.0–13.0)	9.0 (5.0–11.0)	9.0 (6.0–11.0)	32.0 (24.0–38.0)	30.5 (23.0–36.0)	31.0 (26.0–35.0)
		Wilcoxon p-value	NS	NS	NS	NS	0.013	0.004
Age at ERT initiation (years)	Overall	*n* (missing)	14 (12)	45 (10)	59 (22)	184 (72)	224 (37)	408 (109)
		Mean (SD)	16.7 (4.1)	15.5 (3.8)	15.8 (3.8)	49.4 (12.7)	45.8 (14.6)	47.4 (13.9)
		Median (95% CI)	15.9 (14.2–22.1)	15.1 (13.4–17.1)	15.6 (14.5–17.1)	50.6 (47.9–52.6)	44.7 (41.0–49.4)	48.0 (46.2–50.5)
	2001–2006	*n* (missing)	8 (4)	18 (5)	26 (9)	72 (35)	81 (7)	153 (42)
		Mean (SD)	17.7 (4.5)	17.5 (3.8)	17.6 (4.0)	49.5 (11.8)	43.2 (14.9)	46.2 (13.8)
		Median (95% CI)	17.1 (14.2–22.9)	17.3 (16.0–19.0)	17.3 (15.8–19.0)	52.2 (47.9–55.2)	40.4 (37.8–46.5)	46.5 (42.5–52.2)
	2007–2013	*n* (missing)	6 (8)	27 (5)	33 (13)	112 (37)	143 (30)	255 (67)
		Mean (SD)	15.3 (3.2)	14.1 (2.8)	14.31 (2.88)	49.31 (13.29)	47.25 (14.28)	48.2 (13.9)

Characteristic	Diagnosis period	Statistics	Girls (n = 26)	Boys (n = 55)	Total children (*n* = 81)	Adult females (*n* = 256)	Adult males (*n* = 261)	Total adults (*n* = 517)
		Median (95% CI)	15.4 (10.7–18.6)	14.4 (12.6–15.4)	14.6 (12.7–15.4)	49.7 (46.9–52.8)	47.6 (43.4–51.5)	48.2 (46.2–51.6)
	Wilcoxon comparison	p-value	NS	0.005	0.003	NS	0.048	NS

CI, confidence interval; ERT, enzyme replacement therapy; SD, standard deviation.
(Missing) indicates the number of patients missing age at diagnosis, symptom onset and ERT initiation