Gastrointestinal Symptoms in 342 Patients With Fabry Disease: Prevalence and Response to Enzyme Replacement Therapy

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Background & Aims: **Fabry disease is an X-linked deficiency of α-galactosidase A, resulting in lysosomal deposition of globotriaosylceramide in nearly all tissues. The disease frequently causes diarrhea and abdominal pain, which are assumed to arise from malfunction of enteric neurons and which mimic diarrhea-predominant irritable bowel syndrome (IBS). There are limited data about the prevalence and nature of gastrointestinal symptoms in patients with Fabry disease and the response to enzyme replacement therapy (ERT) in large cohorts. The aims of this study were to evaluate the nature and prevalence of gastrointestinal symptoms and their impact on health-related quality of life (HRQoL) in patients with Fabry disease and to analyze changes after 12 and 24 months of treatment with agalsidase alfa.** ***Methods:*** **Information about gastrointestinal symptoms was obtained from regular interviews before and during the time of ERT. Data on HRQoL were collected by using the EQ-5D questionnaire.** ***Results:*** **The overall prevalence of gastrointestinal symptoms was 52%, with abdominal pain and diarrhea being most frequent. Female patients were more frequently affected than male patients, and there was a high prevalence in children (abdominal pain, 49.3%; diarrhea 25.4%). ERT with agalsidase alfa reduced the prevalence of abdominal pain, with a statistically significant decrease in male patients and in children after 12 months of treatment.** ***Conclusions:*** **The gastrointestinal symptomatology of Fabry disease is very similar to diarrhea-predominant IBS; however, pathophysiologic similarities remain to be elucidated. ERT reduced the prevalence of gastrointestinal symptoms in Fabry disease, particularly in children and male patients.**

Fabry disease (Online Mendelian Inheritance in Man database 301500) is an X-linked inborn error of metabolism caused by deficiency of α-galactosidase A, with an estimated incidence between 1:40,000–1:117,000.[1,2] The biochemical consequence is a progressive lysosomal accumulation of globotriaosylceramide in nearly all organ systems. The clinical manifestations of Fabry disease typically begin in childhood with acroparesthesia and angiokeratoma. Corneal opacities and microalbuminuria might also be observed.[3] With advancing age, vital organs are increasingly affected, and the major causes of death are cerebrovascular events, myocardial infarction, and progressive renal insufficiency. Untreated male patients with Fabry disease have an estimated life expectancy of approximately 50 years.[4] Initially, heterozygous females were considered to be asymptomatic carriers; however, it is now apparent that they do exhibit symptoms of Fabry disease, with appreciable morbidity and mortality.[5,6] Enzyme replacement therapy (ERT) for Fabry disease was approved in 2001 and has been reported to be well-tolerated and effective.[7–9]

Previous reports suggest a prevalence of gastrointestinal symptoms of up to 70% in cohorts of patients with Fabry disease. Reported symptoms include abdominal cramps, nausea and vomiting, and both diarrhea and constipation.[10] Anecdotal reports also document cases of progressive weight loss associated, in part, with severe postprandial pain.[11,12] Nocturnal diarrhea and fecal incontinence occur, with profoundly negative effects on social and economic functioning and quality of life.[13] Case reports and series suggest gastrointestinal function improves soon after the introduction of ERT.[12,14,15] However, this has not been systematically studied in a large cohort of patients.

We report here on the prevalence and nature of gastrointestinal symptoms in 342 patients with Fabry disease enrolled in the Fabry Outcome Survey (FOS). Data on prevalence and changes in symptomatology 12 and 24 months after the introduction of ERT are analyzed, as well as the impact of gastrointestinal symptoms on health-related quality of life (HRQoL).

Methods

Patients and Data Collection

FOS is an open international database for patients with a confirmed diagnosis of Fabry disease. The properties and management of the database have been described previously.[3] Briefly, patients are evaluated on symptoms of 16 different organ systems by simple questions during regular visits at their treatment centers. Questions on gastrointestinal symptoms include the manifestation of abdominal pain (its nature, frequency, precipitants) as well as the occurrence of nausea, constipation, vomiting, and diarrhea ("Do you suffer from . . .?"). In addition, patients are asked whether there was a diagnosis of gastritis/ulcer, pancreatitis, hemorrhoids, or other gastrointestinal disorder made by a physician at any time during their medical history. Data collection is on a voluntary basis and is not linked to continued provision of ERT, being aware that this

Abbreviations used in this paper: BMI, body mass index; ERT, enzyme replacement therapy; FOS, Fabry Outcome Survey; HRQoL, health-related quality of life; IBS, irritable bowel syndrome.

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Table 1. Demographics of Patients Enrolled in the FOS by October 2005

	Total	Male	Female	Adults	Children
No. of patients in FOS by October 2005	714	345	369	587	127
No. of patients					
With information on GI symptoms	342	139	203	271	71
Without information on GI symptoms	372	206	166	318	54
Age (*y*; mean ± SD)					
With GI symptoms	35.0 ± 17.6	32.3 ± 16.9	36.9 ± 17.9	41.3 ± 13.9	10.9 ± 5.0
Without GI symptoms	35.2 ± 15.7	34.3 ± 13.4	36.4 ± 18.0	39.3 ± 12.9	10.9 ± 4.1
Height (*cm*; mean ± SD)					
With GI symptoms	162.6 ± 18.2	165.6 ± 22.3	160.5 ± 14.2	168.2 ± 8.8	142.3 ± 26.8
Without GI symptoms	167.4 ± 14.5	172.4 ± 13.3	160.5 ± 13.2	170.8 ± 8.8	144.9 ± 22.7
Weight (*kg*; mean ± SD)					
With GI symptoms	65.2 ± 19.5	62.8 ± 21.6	62.4 ± 17.9	68.7 ± 14.2	40.4 ± 20.1
Without GI symptoms	65.7 ± 16.2	67.8 ± 16.3	62.8 ± 15.7	69.3 ± 12.7	41.8 ± 16.4
BMI (kg/m^2; mean ± SD)					
With GI symptoms	23.0 ± 5.2	21.9 ± 4.3	23.8 ± 5.7	24.3 ± 4.9	18.4 ± 3.8
Without GI symptoms	23.2 ± 4.5	22.5 ± 4.1	24.1 ± 4.9	23.8 ± 4.3	19.2 ± 4.2

GI, gastrointestinal; SD, standard deviation.

might affect follow-up. Data are collected anonymously, entered into the database by clinical staff in their respective institutions, and stored centrally. Data collected in FOS are derived from patients' medical histories as well as regularly completed questionnaires regarding pain and HRQoL. HRQoL is evaluated by using the EQ-5D questionnaire.[16] Additional information about the patient's health state and a broad range of laboratory parameters are entered by physicians or nurses. The FOS database has been approved by the Ethics Institution Review Board of all participating centers, and all patients provided written informed consent.

Data Analysis and Statistics

Cross-sectional analysis of reported symptoms and age of onset was performed. For patients who were symptomatic at entry into FOS, age at onset of symptoms was taken from the patient's report of the first manifestation of each symptom. For patients who did not report symptoms at entry into FOS but who developed and reported such complaints later, age at onset was recorded accordingly. Longitudinal analysis of reported symptoms was based on a subset of patients for whom data were available at 12 ± 3 and 24 ± 3 months after initiation of ERT. Data are presented as mean ± standard deviation; age at onset is reported as median ± standard deviation. Significance testing for improvement of gastrointestinal symptoms in patients receiving ERT was performed with McNemar test for paired binomial data.

Changes in quality of life data were analyzed with the signed rank test. Any group comparison of quality of life was done with Wilcoxon rank sum test. Children were excluded from the evaluation of HRQoL, because reliable reference data for the EQ-5D are only available for adults.

Results

At the time of this analysis (October 2005), 752 patients had been enrolled in the FOS database from 11 countries in Europe. Clinical data on signs and symptoms of Fabry disease were available in 714 individuals (369 female and 345 male) including 127 children younger than the age of 18 years (70 girls, 57 boys). Patient characteristics are summarized in Table 1. Of these, 342 patients had documented information about gastrointestinal symptoms and had not been treated with ERT before or at the time of entering the FOS database. Notably, these patients were not different from those in whom gastrointestinal information was not available (Table 1).

Prevalence and Nature of Gastrointestinal Symptoms in Patients With Fabry Disease

Figure 1 illustrates the nature and prevalence of gastrointestinal symptoms in the 342 patients evaluated. The overall prevalence of gastrointestinal complaints was 52.0% (n = 178). Interestingly, female patients reported gastrointestinal symp-

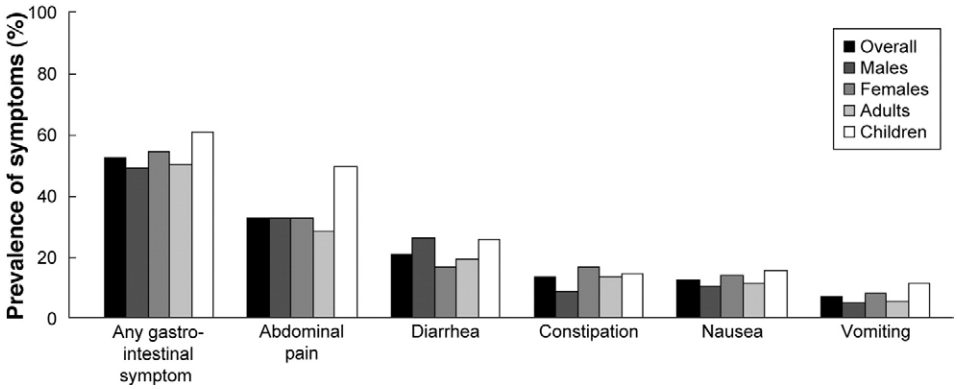

Figure 1. Reported prevalence of gastrointestinal symptoms in 342 patients with Fabry disease: more than 50% of patients with Fabry disease reported gastrointestinal symptomatology before the initiation of ERT. The most prevalent symptoms were abdominal pain and diarrhea.

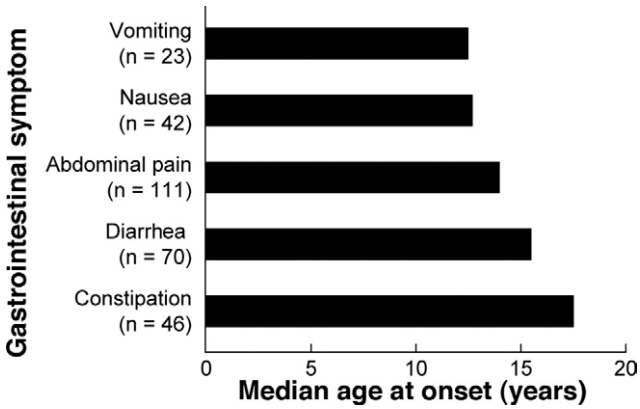

Figure 2. Median age at onset of gastrointestinal symptoms in 292 patients with Fabry disease. Gastrointestinal symptoms were reported at an early stage. For comparison, mean age of onset of acroparaesthesia, as the leading symptom in Fabry disease, is 9 years.

toms more often than male patients (54.2% vs 48.9%), and children reported symptoms more frequently than adults (60.8% vs 49.8%).

Abdominal pain. The most prevalent gastrointestinal symptom was abdominal pain, which was present in 32.5% of the evaluated patients (Figure 1). There was no difference in the prevalence between male and female patients. Children reported abdominal pain more frequently than adults (49.3% vs 28.0%). Consistent with this, the median age at onset of abdominal pain was 14.0 years (range, 0–69 years; Figure 2).

Diarrhea. Diarrhea was reported in 20.5% of the patients with documented information on gastrointestinal symptoms. There was a marked difference between male (25.9%) and female patients (16.7%; Figure 1). Similar to abdominal pain, diarrhea was more frequently reported in children than in adults (25.4% vs 19.2%; Figure 1). The median age at onset of diarrhea was 15.5 years (range, 0–60 years).

Constipation. Constipation was reported as a gastrointestinal symptom in 13.5% of the 342 evaluable patients. In contrast to diarrhea, constipation was nearly twice as frequently reported by female patients as by male patients (16.7% vs 8.6%; Figure 1). Moreover, constipation was equally prevalent in children and adults (13.3% and 14.1%, respectively; Figure 1). The median age at onset of constipation was 17.5 years (range, 0–66 years; Figure 2).

Nausea and vomiting. The reported prevalence of nausea in this population of patients with Fabry disease was 12.3%, and there were minor differences between male and female patients (13.8% vs 10.1%; Figure 1). A higher proportion of children than adults reported nausea (15.5% vs 11.4%; Figure 1), and the median age at onset of nausea and vomiting was 12.7 years and 12.5 years, respectively (Figure 2). Vomiting was reported by a minority of patients (6.7%). There were fewer female than male patients with vomiting (7.9% vs 5.0%). The prevalence of nausea and vomiting in children was about twice that observed in adults (Figure 1).

Other gastrointestinal symptoms. FOS also collects data on the presence of other gastrointestinal symptoms. Of the 342 patients evaluated, 29 (8.5%) reported hemorrhoids, 15 (4.4%) reported gastritis or ulcer, and 3 (0.9%) reported pancreatitis.

Symptom combinations. The most frequently observed combination of gastrointestinal symptoms in patients with Fabry disease was abdominal pain and diarrhea (14.3%), followed by abdominal pain and nausea (9.4%), and abdominal pain and constipation (7.3%).

Body Mass Index

The mean body mass index (BMI) of children in FOS was 18.4 kg/m^2, which is equal to values between the 50th and the 75th percentiles.[17] There were no differences in BMI between children with and without gastrointestinal complaints (18.2 vs 18.8 kg/m^2). A similar result was observed in adult patients. Those with gastrointestinal manifestations had a mean BMI of 24.7 kg/m^2, whereas those without gastrointestinal symptoms had a mean BMI of 23.9 kg/m^2.

Use of Medications for Gastrointestinal Symptoms

The use of medications for gastrointestinal symptoms was recorded for only 8 patients in the database, and we have therefore not undertaken any further analysis of these data.

Relationship Between Gastrointestinal Symptoms and Quality of Life

At baseline, data on HRQoL were available for 108 patients (41 male, 67 female). The mean EQ-5D score in this cohort was 0.69. However, patients with gastrointestinal symptoms (n = 65) had significantly lower EQ-5D scores than patients without gastrointestinal symptoms (n = 43; 0.63 vs 0.78; $P < .05$). Patients with diarrhea had lower EQ-5D scores compared with those without diarrhea (0.56 vs 0.61; P = not significant).

Changes in Gastrointestinal Symptoms After Twelve Months of Enzyme Replacement Therapy

Data on abdominal pain were available for 62 patients at baseline and after 12 months of ERT (14 children, 48 adults; 21 females, 41 males; Figure 3). Abdominal pain was reported by 49% of the patients at baseline and by 39% 12 months after initiation of ERT. Changes were similar in male and female

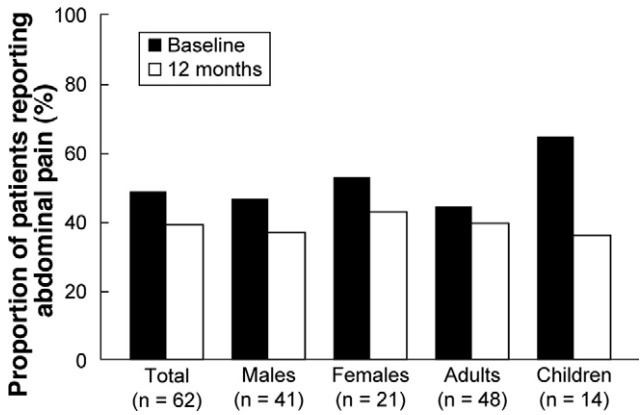

Figure 3. Reported changes in prevalence of abdominal pain after 12 months of ERT with agalsidase alfa; *numbers in brackets* represent the number of evaluable patients with relevant data on gastrointestinal symptomatology at baseline and after 12 months of therapy.

patients (10% in both subgroups). Notably, the prevalence of abdominal pain in children was reduced from 64% to 36% after 12 months of treatment. During the same period, the frequency in adults fell from 44% to 40% (Figure 3). Overall, improvements were significant in male patients ($P < .05$) and in children ($P < .05$). Interestingly, efficacy tables revealed that there were no male patients and no children reporting abdominal pain for the first time after 12 months of ERT (data not shown).

Data on diarrhea at baseline and after 12 months of ERT were available in 60 individuals (12 children, 48 adults; 21 females, 39 males). At baseline, 27% of these patients reported diarrhea, and the prevalence was reduced by 8% after 12 months (Figure 4). Interestingly, improvement was more pronounced among male than female patients (10% vs 5%). The prevalence in children was significantly reduced from 36% to 7% after 12 months of ERT ($P < .05$), whereas changes in the other subgroups did not reach statistical significance. In addition, no child reported diarrhea for the first time after starting ERT (data not shown).

Data on changes of HRQoL after 12 months of treatment with agalsidase alfa were available in 33 patients. Mean EQ-5D scores slightly improved from 0.65 ± 0.35 to 0.69 ± 0.31 in patients with gastrointestinal symptoms after 12 months and from 0.72 ± 0.23 to 0.77 ± 0.23 in patients without gastrointestinal complaints (not significant). The improvement in EQ-5D scores was entirely attributable to male patients, because female patients maintained an EQ-5D score of 0.70 ± 0.34, whereas scores in male patients changed from 0.55 ± 0.34 to 0.68 ± 0.29 (not significant). A trend for improved EQ-5D scores was also seen in patients with diarrhea, increasing overall from 0.59 ± 0.32 to 0.68 ± 0.26 (not significant).

Changes in Gastrointestinal Symptoms After Twenty-four Months of Enzyme Replacement Therapy

Data on abdominal pain were available for 58 patients at baseline and after 24 months of ERT (10 children and 48 adults; 25 females, 33 males). The prevalence of abdominal pain at baseline was 43%, and only 29% reported this symptom after 24 months of ERT ($P < .05$). Interestingly, in female patients the prevalence of abdominal pain was reduced from 40% to 20%, whereas improvements in male patients were less striking (45% vs 36%). Thirty-five percent of adult patients reported abdominal pain at baseline, whereas the prevalence was reduced to 25% after 24 months of treatment. The reduction in frequency of reported abdominal pain was more striking in children, in whom the prevalence was reduced from 80% to 50% after 24 months of ERT (Figure 5). Notably, no child reported abdominal pain as a new symptom during 24 months of ERT (data not shown).

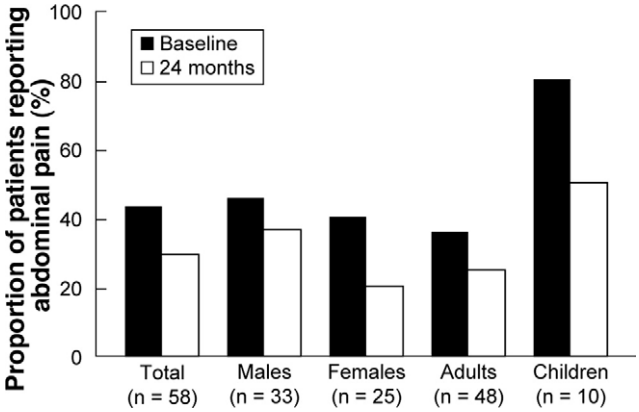

Figure 5. Reported changes in prevalence of abdominal pain after 24 months of ERT with agalsidase alfa; *numbers in brackets* represent number of evaluable patients with relevant data on gastrointestinal symptomatology at baseline and at 24 months.

Information on diarrhea was available in the FOS database at baseline and after 24 months of ERT for 57 patients. This group comprised 25 female and 32 male patients, including 11 children (Figure 6). At baseline, the prevalence of diarrhea was 28%, and after 24 months of ERT this was reduced to 26% (Figure 6). In the subgroup of male patients, 41% of patients reported diarrhea at baseline and 34% after 24 months of treatment. In contrast to this, the prevalence of diarrhea in female patients (12% vs 16%) and adults (24% vs 26%) was higher after 2 years of ERT compared with baseline. However, in children, the prevalence was markedly reduced from 45% to 27%. Finally, only 5% of the patients who did not complain

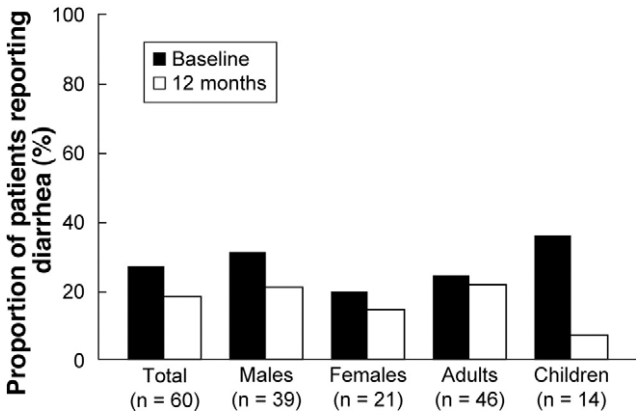

Figure 4. Reported changes in prevalence of diarrhea after 12 months of ERT with agalsidase alfa; *numbers in brackets* represent number of evaluable patients with relevant data on gastrointestinal symptomatology at baseline and at 12 months.

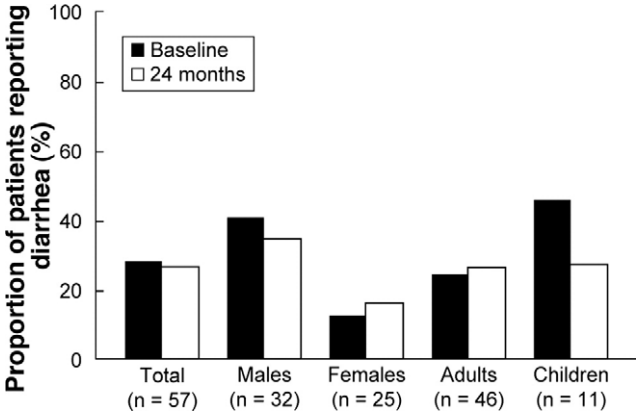

Figure 6. Reported changes in prevalence of diarrhea after 24 months of ERT with agalsidase alfa; *numbers in brackets* represent number of evaluable patients with relevant data on gastrointestinal symptomatology at baseline and at 24 months.

about diarrhea at baseline developed this symptom after 24 months of ERT (data not shown).

EQ-5D data after 24 months of treatment with agalsidase alfa were available in 18 patients (12 male, 6 female). In these patients, HRQoL improved from 0.63 ± 0.37 to 0.71 ± 0.31 (not significant).

Discussion

Fabry disease is a rare multisystemic inherited metabolic disease with profound effects in almost all organ systems, reduced life expectancy,[4] and substantial involvement of the gastrointestinal tract.[11,18–25] However, most reports are based on single cases or small cohorts. A larger cohort of patients was described by MacDermot et al,[4] who reported a prevalence of approximately 70% for gastrointestinal symptoms in 98 male patients with Fabry disease. In this report, the predominant gastrointestinal symptoms were abdominal pain and diarrhea, and there was no information regarding gastrointestinal symptoms in female patients or children with Fabry disease. Reports on the effects of ERT on gastrointestinal symptoms were limited to small numbers of treated patients.[12,14,15]

We have analyzed 714 unselected symptomatic adults and children with Fabry disease in FOS. Follow-up of these patients during more than 24 months has allowed longitudinal analyses of changes during ERT. The overall prevalence of gastrointestinal symptoms in 342 patients in the FOS database from whom data on gastrointestinal symptoms were available was 52% (male patients 54%, female patients 49%), which is lower than previously reported.[4,21,26] A potential explanation for this discrepancy is under-reporting of symptoms, because the data within FOS are based on information obtained from the medical history at baseline. The reporting of symptoms in this context is spontaneous rather than elicited by direct questioning, and patients with long-standing symptoms might accommodate their condition and have a lower perception of ill health. Furthermore, FOS includes clinically affected individuals as well as biochemically deficient patients with minimal overt symptomatology. We also cannot exclude a selection bias in favor of patients with gastrointestinal symptoms. More than 50% of the patients enrolled in the database at the time of these analyses provided no information regarding gastrointestinal symptoms.

There are some gender differences in the reported prevalence of gastrointestinal complaints in patients with Fabry disease, eg, constipation was reported in 16.7% of the female patients and 8.6% of the male patients. However, there are gender differences reported also in the literature regarding bowel habits and gastrointestinal symptoms in the general population.[27,28] Hence, the differences observed here might reflect the situation in the general population on a higher prevalence level caused by the underlying disease in these patients.

The prevalence of gastrointestinal symptoms in children younger than the age of 18 years is markedly higher than in adults, although this is less than previously described in the literature on pediatric Fabry disease.[29,30] The most prevalent gastrointestinal symptom in children was abdominal pain (49%). For comparison, healthy individuals had a prevalence of 12.3% for abdominal pain, 19.2% for diarrhea, and 19.9% for constipation.[31] These data suggest that abdominal pain and diarrhea might be directly related to Fabry disease rather than reflecting the average probability of developing gastrointestinal symptoms. It remains speculative why the reported prevalence for abdominal pain in adults is lower than in children. One possible explanation might be that patients with a long history of a certain complaint might under-report this symptom.[32] Whether the lower prevalence of gastrointestinal symptoms in adult patients with Fabry disease is part of the natural course of the disease needs further elucidation in prospective studies.

The assumption that abdominal pain and diarrhea might be directly related to Fabry disease is supported by the age at manifestation of abdominal pain, which is 14.0 years (Figure 2) and therefore is close to the age at manifestation of acroparesthesia. In only 3 patients, all of whom were children, was a gastrointestinal symptom the sole potential manifestation of Fabry disease. Hence, these data indicate that the gastrointestinal tract might be affected early in the course of Fabry disease.

Gastrointestinal symptoms in Fabry disease do also impact on HRQoL. EQ-5D scores in patients with gastrointestinal symptoms at baseline were significantly lower than in patients without such complaints. Because abdominal pain is the major gastrointestinal symptom in patients with Fabry disease, "pain/discomfort" as a dimension of the EQ-5D is not an independent variable. However, it is not feasible to evaluate HRQoL disregarding the impact of pain on the individual's situation.

Twelve and 24 consecutive months of ERT with agalsidase alfa had beneficial effects on gastrointestinal symptoms. Improvements were particularly noted for abdominal pain (predominantly male patients and children, Figures 3 and 5) and diarrhea (Figures 4 and 6). In the subgroup of patients with information on gastrointestinal symptoms at baseline and after 24 months of ERT, 25 patients reported abdominal pain at baseline, but only 15 of these patients still reported abdominal pain after 24 months. In addition, at baseline, the predominance of gastrointestinal improvements in children under ERT also during a period of 24 months suggests that these changes might not be related to placebo effect rather than to the application of the missing enzyme in Fabry disease. ERT might have a preventative role in the development of gastrointestinal symptoms. For instance, no child without abdominal pain at baseline developed this symptom during 24 months of ERT. Thus, early treatment of asymptomatic or mildly symptomatic patients might be justified to prevent progression. However, a final statement on such preventive effects of ERT in children needs confirmation on a larger cohort of patients in the young age group under treatment followed during a longer period of time.

Reports of marked weight loss in patients with Fabry disease and gastrointestinal symptoms[4,11,12,15] are not confirmed by the data presented here. The BMI was in the normal range irrespective of the presence or absence of gastrointestinal symptoms, and there was no evidence of any deficiency of specific nutrients in the biochemical and hematologic data held in FOS (data not shown). Thus, the high prevalence of gastrointestinal symptoms is not accompanied by organic intestinal disease or malnutrition. In this respect, the gastrointestinal features of Fabry disease closely resemble functional gastrointestinal disorders such as irritable bowel syndrome (IBS).[21] However, it remains open whether abdominal pain in IBS is caused by neuropathy, too.

Gastrointestinal symptoms in patients with Fabry disease have a profound impact on HRQoL. Patients with Fabry disease and gastrointestinal symptoms had a significantly lower EQ-5D

score at baseline compared with patients without gastrointestinal manifestations. In addition, patients with diarrhea had lower EQ-5D scores compared with those without diarrhea, although this difference was not statistically significant.

Changes of EQ-5D were not significant after 12 and 24 months, respectively. However, the number of patients with available information during treatment was relatively low and might limit this subanalysis. In addition, we cannot exclude the fact that overall improvements of quality of life lead also to improved perception of gastrointestinal functions. However, such an effect might be lessened during a period of more than 2 years of follow-up.

These data, on the basis of a large cohort of patients, strongly suggest improvements in gastrointestinal function that could have a major positive effect on quality of life for patients with Fabry disease. The mechanisms whereby improvements in gastrointestinal symptomatology in patients with Fabry disease occur remain unknown. Light and electron microscopic investigations of the gastrointestinal tract demonstrated lipid deposition within ganglion cells of the enteric nervous system.[18,19,24,33] There is also evidence for altered intestinal motility in Fabry disease.[18,19,22,23] In addition, small mesenteric vessels might show cytoplasmic deposition of glycosphingolipids, and it has been suggested that microvascular ischemia is implicated.[23]

Thus, dysfunction of enteric neurons, intestinal dysmotility, and microvascular changes might all be relevant in the pathophysiology of gastrointestinal symptoms in Fabry disease. Furthermore, there is no evidence of increased inflammatory activity in the intestine in Fabry disease. Therefore, gastrointestinal involvement in Fabry disease in part is reminiscent of diarrhea-predominant IBS. It will be interesting to determine in prospective studies whether improvements in gastrointestinal function, as a consequence of ERT, can be correlated with alterations in the morphology and function of enteric nerves and the microvasculature, or whether the improvements reported by affected patients are achieved by functional alterations. Notably, there are reports of improvements in other neurologic symptoms with ERT, eg, peripheral nerve function,[34,35] neuropathic pain,[36] and hearing.[37,38]

Strength and Limitations of This Study

This study is an open observational study rather than a prospectively planned investigation. Therefore, no comparison group was included in this study, and differences between subgroups of patients have to be discussed carefully.

The definitions of gastrointestinal symptoms in the context of the FOS database before this analysis were not predefined, and information collected is based on reports by patients, rather than on biochemical markers or the results of investigations.

Because data collection was not linked to the availability of ERT, the loss of follow-up data is considerably large. Nevertheless, this study on gastrointestinal symptoms in patients with Fabry disease is based on a large, unselected cohort of patients under both conditions, without and with treatment of Fabry disease by ERT.

Appendix 1

The data in this study were provided by the European FOS Investigators Group:

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