CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2013: 83: 432–438
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Published by Blackwell Publishing Ltd
CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2012.01947.x

Original Article

Fabry disease in children: agalsidase-beta enzyme replacement therapy

Borgwardt L, Feldt-Rasmussen U, Rasmussen AK, Ballegaard M, Meldgaard Lund A. Fabry disease in children: agalsidase-beta enzyme replacement therapy.
Clin Genet 2013: 83: 432–438. © John Wiley & Sons A/S. Published by Blackwell Publishing Ltd, 2012

Fabry disease is a rare, multiorgan disease. The most serious complications involve the kidney, brain and heart. This study aims to assess the effect of enzyme replacement therapy (ERT) using agalsidase-beta in children with Fabry disease. We carried out a nationwide, descriptive and observational retrospective cohort study of 10 children (9–16 years at baseline), who underwent regular systematic investigations for 1–8 years after initiation of ERT with agalsidase-beta (Fabryzyme®, Genzyme). Ophthalmological, echocardiographic abnormalities and hypohidrosis were found at baseline and during the follow-up period. Serious kidney, heart or brain involvement had not developed at the last follow-up examination. For the majority of the patients improvements were found concerning headache, acroparaesthesias and gastrointestinal pain during the follow-up period. The level of energy and physical activity also increased. Treatment with agalsidase-beta was associated with a reduction of neuropathic and abdominal pain and headache. Although all aspects of the Fabry pain phenotype cannot be treated with ERT, the observed effects were clinically significant in the lives of the majority of Fabry children and together with the absence of serious Fabry manifestations at last follow-up, we argue that early initiation of ERT may be considered.

Conflict of interest

We have no conflicts of interest to declare.

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Key words: agalsidase-beta – enzyme replacement therapy – Fabry – pain

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Received 13 June 2012, revised and accepted for publication 2 August 2012

Fabry disease is a rare, multiorgan disease. The most serious complications involve the kidney, brain and heart, leading to end-stage renal disease, cerebrovascular events and progressive hypertrophic cardiomyopathy, arrhythmias and valvular disease. Typical presenting symptoms start in childhood and early adolescence and are neuropathic extremity pain, abdominal pain, headache, fatigue and hypohidrosis that frequently lead to decreased exercise tolerance and may reduce quality of life and school attendance in children (1).

Enzyme replacement therapy (ERT) is the only specific therapy for Fabry disease. Two formulations are available; agalsidase-alfa (Replagal®, Shire Human Genetic Therapies, Inc., Cambridge, MA) and agalsidase-beta (Fabrazyme®, Genzyme Corporation, Inc, Cambridge, MA). Experience with ERT in Fabry children is limited to a few clinical studies and case reports (2–10). The longest period of follow-up was 4 years documenting sustained reduction of neuropathic pain (8). The majority of the published studies were small or case reports and were using agalsidase-alfa as ERT (2, 5–9, 11). Only two studies were using agalsidase-beta as ERT (3, 10).

The primary objective of this study was to assess efficacy and safety of ERT using agalsidase-beta in children and adolescents with Fabry disease. The study was a descriptive and observational retrospective assessment.

Materials and methods

Ten children and adolescents with Fabry disease were given ERT at the Centre for Inherited Metabolic Disorders, Copenhagen University Hospital, Rigshospitalet, Denmark in the study period from March 2003 to July

2011. Fabry disease was confirmed in all patients by *GLA* mutation analysis. All patients underwent regular systematic examinations for manifestations of Fabry disease as a part of the normal follow-up procedure at the hospital. All patients with Fabry disease started the regular systematic examinations when diagnosed to define the child's manifestations of Fabry disease and to help decide the proper time to start the ERT. The regular systematic examinations were also performed to monitor the efficacy of the treatment, in part to justify the expensive treatment in relation to health authorities.

A review of all data for a maximum follow-up period of 8 years was performed. The following data were collected: subjective symptoms using a visual analogue scale (VAS)-scoring instrument (described below) and results of objective examinations including full physical examination, height, weight, cardiac examination, kidney investigations (Chrom-EDTA clearance (12), urine excretion of albumin/protein in spot urine samples and renal ultrasound), neurological investigations including brain magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning (13, 14), ophthalmologic examination, pure tone audiometry, sweat conductivity (15) and measurements of serum globotriaosylceramide (Gb_3) and urine Gb_3 (16) and electrophysiological studies and tests for autonomic dysfunction (17). Because of the lack of patient or parent consent, the electrophysiological studies and tests for autonomic dysfunction were not performed systematically for all of the children and the results of these studies are not described in this article.

Cardiac examination included clinical examination, a standard 12-lead electrocardiography (ECG) and a two-dimensional echocardiography (ECHO).

Gb_3 was tested in plasma and urine sediments by Department of Radiation Physics, Sahlgrenska University Hospital, Sweden. Plasma Gb_3 or globotriaosylceramide (GL_3) was expressed as an absolute concentration [(Gb_3 (μmol/l) or GL_3 (μg/ml)] and urinary Gb_3 as a ratio in relation to sphingomyelin excretion (mol/mol) or creatinine excretion (μmol/mol). Reference values for plasma concentrations were: Gb_3 1.6–3.3 μmol/l, and $GL_3 \leq 7$ μg/ml. Reference values for urinary Gb_3:sphingomyelin ratio: <0.3 mol/mol, for Gb_3:creatinine ratio <10 μmol/mol (18).

All results were assessed in relation to relevant age-corrected reference intervals.

Subjective symptoms recorded included reports of acroparaesthesias, abdominal pain/discomfort and level of energy, which was scored using a VAS scoring instrument with increasing severity of symptoms from 0 to 10 as experienced on average during the last week. The scoring was performed according to Varni–Thompson paediatric pain questionnaire and Mills et al. (3). Headache was recorded as number of episodes during the last month. Physical exercise (PE) performance was scored as very bad (4), bad (3), fair (2) and good (1).

The same physician, AL, did the scoring of subjective symptoms every 4–6 months during the study period. The clinical examinations and follow-up programme were performed yearly. In this study, examinations at baseline (at the time the patients started treatment with agalsidase-beta), after 1 year, after 3–4 years and after 5–8 years of treatment will be reported.

Agalsidase-beta (Fabrazyme), 1 mg/kg was given intravenously every other week through a peripheral catheter in seven children and through a Port-a-Cath in three children. The Port-a-Caths were removed after 2–3 years in all three children due to infection (one patient) or patient requests (two patients). Because of a shortage of agalsidase-beta (Fabryzyme) in 2010/2011, 6 of the 10 patients subsequently received agalsidase-alfa (Replagal).

Safety evaluation

As this study was not a clinical trial, the safety assessments are based on registration of infusion related reactions (IRR), vital signs during the infusions and adverse events in the study period. Anti-agalsidase-beta antibodies were not routinely analysed.

Routine antipyretic/antihistaminergic premedication was not given.

Statistics

The study was a descriptive observational retrospective assessment with a small cohort of 10 patients, where no attempt of formal statistical analysis has been carried out. Mean values, including minimum and maximum values are mentioned.

Results

Ten patients (six boys and four girls) from seven different families were included. Nine patients came from Fabry families with severe classical disease manifestations and one boy was diagnosed at age 13 as the first in his family. His family history included maternal acroparaesthesias since childhood and renal insufficiency in his uncle, but no history of early deaths secondary to heart-, kidney- or brain complications.

Patient characteristics at baseline, including onset of symptoms, diagnosis, age at start of treatment, ethnicity and mutations, are described in Table 1.

Objective evaluations

The results of albumin/creatinine ratio, protein/creatinine ratio, glomerular filtration rate (GFR) by Chrom-EDTA-clearance, ECHO/ECG studies, sweat tests and ophthalmological examinations are summarized in Table 2.

Estimation of GFR by Chrom-EDTA-clearance, ultrasound of the kidneys, MRI-cerebrum, PET-cerebrum, audiometry, albumin/creatinine ratio and protein/creatinine ratio were normal at baseline and in the follow-up period for all patients, except one boy who had an increased albumin/creatinine ratio at baseline, which became normal during follow-up.

Table 1. Patient characteristics at baseline concerning onset of symptoms, diagnosis, age at start of treatment, ethnicity and mutations

Patient number	Sex	Age at first onset of symptoms (years)	Age at diagnosis (years)	Age at start of treatment (years)	Ethnicity	α-Galactosidase A activity	Mutation
1[a]	M	2	3	14	Caucasian	1.1 (18–54)[d]	p.N34S (c.1280A>G)
2[a]	M	3	5	16	Caucasian	ND	p.N34S (c.1280A>G)
3	M	6	0	10	Caucasian	ND	p.G85N (c.5153G>A)
4[b]	F	5	8	10	Caucasian	ND	p.G85N (c.5153G > A)
5[b]	M	1	1	12	Caucasian	1.0 (18–54)[d]	p.G85N (c.5153G>A)
6[c]	F	9	11	12	Caucasian	ND	p.R227X (c.10170C>T)
7[c]	F	7	10	11	Caucasian	ND	p.R227X (c.10170C>T)
8	M	3	13	13	Caucasian	1.4 (18–54)[d]	c.10684delA
9	M	7	9	9	Caucasian	2.8 (18–54)[d]	p.G271S (c.811G>A)
10	F	7	13	16	Caucasian	ND	p.G85D (c.5153G>A)

[a]Patients 1 and 2 are siblings.
[b]Patients 4 and 5 are siblings.
[c]Patients 6 and 7 are siblings.
[d]Ref. values: 18–54 unit/mg protein.
ND: Not done.

Concerning GFR measurements neither low values nor signs of hyperfiltration were found.

Cardiac examination

At baseline, one male patient had echocardiographic evidence of mild left ventricular hypertrophy and one female had mild pulmonary and tricuspid valve insufficiency; both had normal 1-year follow-up examinations. Six patients, three males and three females, developed valvular involvement during the follow-up period at age 6–21 years (females 6–15, males 9–21). None of the patients had subjective symptoms from the heart. The first ECHO examination with an abnormal result was performed between ages 6–21 years (Table 2). All electrocardiographic recordings were without abnormalities during the study period.

Sweat testing

Four males had low sweat production at baseline. They all improved with increasing sweat production during the study period. None of them achieved values within the reference range (Table 2).

Ophthalmological examination

At baseline seven patients had cornea verticillata. During the study 9 of 10 patients developed cornea verticillata. No influences on the visual acuity were reported.

Results of measurements of plasma Gb_3 (μmol/l) or GL_3 (μg/ml) were available in 6 of 10 patients. Three of five males had increased concentrations of Gb_3 at baseline (7.6–9.7 μmol/l) (ref. values: 1.6–3.3 μmol/l); one female had slightly elevated concentration of Gb_3 at baseline (3.9 mol/l). Plasma concentrations decreased to the normal range after 2–33 months of treatment.

Gb_3 measurements in urine were available in four males and four females. All four males had increased ratios at baseline. For male patients, three had increased Gb_3:sphingomyelin ratio between 1.5–7.7 mol/mol (ref. values: <0.3 mol/mol), decreasing towards normal range after 5–27 months. One had increased Gb_3:creatinine ratio at 139 μmol/mol (ref. values: <10 μmol/mol) with increasing values during the follow-up. For female patients, three had normal Gb_3:creatinine ratio, one had slightly increased Gb_3:creatinine ratio at baseline (25.7 μmol/mol), which normalized during the follow-up period.

Subjective symptoms

All patients were symptomatic at baseline and had at least two of the symptoms: neuropathic pain, exercise intolerance and gastrointestinal symptoms.

Scorings of subjective symptoms can be seen in Figs 1–3 and Table 2.

Acroparaesthesias

Mean scores at baseline, 12 months, 36 months and at last follow-up were in boys: 6.5, 2.1, 1.8, 1.0, respectively, in girls: 6.6, 2.8, 3.5, 2.5, respectively and in boys and girls combined 6.6, 2.4, 2.7, 1.5, respectively. All patients reported acroparaesthesias at baseline, eight had decreasing symptoms during the study period and two patients had a moderate increase in symptoms after an initial improvement.

Abdominal pain

Mean scorings of abdominal pain at baseline, 12 months, 36 months and at last follow-up were in boys: 4.0, 0.2, 1.1, 0.3, respectively, in girls: 3.3, 2.1, 0.8, 2.5, respectively and in boys and girls combined: 3.7, 0.9, 1.0, 1.0, respectively. Seven of ten patients

Table 2. Results of assessments at baseline, 1 year, 3–4 years and 5–8 years of follow-up:

	Follow-up (years)	Subject 1 (M)	Subject 2 (M)	Subject 3 (M)	Subject 4 (F)	Subject 5 (M)	Subject 6 (F)	Subject 7 (F)	Subject 8 (M)	Subject 9 (F)	Subject10 (M)
U-Albumin/creatinine ratio (mg/mmol)[b]	Baseline	1.6	1.4	0.3	0.6	4.2	[a]	0.4	1.0	1.4	0.5
	1	0.24	0.9	0.3	#	1.67	[a]	0.6	0.4	7.4	#
	3–4	0.4	0.8	0.8	0.4	0.4	0.2	0.5	*	*	*
	5–8	0.3	#	2.2	#	#	0.26	1.8	*	*	*
U-Protein/creatinine ratio (g/mmol)	Baseline	0.01	0.01	0.01	0.01	#	[a]	#	#	0.02	0.01
	1	#	#	0.01	#	#	[a]	0.01	0.01	0.02	#
	3–4	0.01	0.01	0.01	#	#	0.01	0.01	*	*	*
	5–8	#	#	0.01	#	#	0.005	0.01	*	*	*
EDTA clearance [ml/(min × 1.73 m^2)]	Baseline	96	110	112	90	107	95	126	114	106	106
	1	105	102	110	100	95	116	124	104	101	123
	3–4	96	112	99	106	97	97	127	*	*	*
	5–8	100	127	115	90	104	96	102	*	*	*
ECHO/ECG	Baseline	N	N	N	N	N	N	N	N	Mild TI, PI	Mild LV hyper-trophy
	1	N	N	#	Mild MI	N	#	N	N	N	N
	3–4	Mild MI, PI, TI	N	N	Mild MI	N	Mild MI	N	*	*	*
	5–8	Mild MI, PI, TI	Mild AI, MI	Mild AI, MI	Mild MI, PI, TI	N	Mild MI	Mild PI	*	*	*
Sweat test (mg/30 min) [c]	Baseline	15	71.3	74.9	44.8	26.1	33.6	64.7	2.2	50.3	6.1
	1	25.9	82.5	#	44.7	45.7	44.6	61.4	3.8	65	8.9
	3–4	27.6	60.2	71.9	46.3	45.7	#	52.3	*	*	*
	5–8	33.6	74.7	106.1	41.2	41.9	#	47.0	*	*	*
Ophthalmological exam	Baseline	CV	CV	N	CV	N	CV	CV	CV	CV	N
	1	CV	CV	CV	CV	CV	CV	CV	CV	CV	N
	3–4	CV	CV	CV	CV, TV	CV	CV	CV	*	*	*
	5–8	CV	CV	#	CV, TV	CV	CV	CV	*	*	*

*, Not available because of the limitation of the study period; #, not performed; CV, cornea verticillata; ECG, electrocardiography; ECHO, two-dimensional echocardiography; LV, left ventricular hypertrophy; MI, mitral insufficiency; N, ECHO/ophthalmological examination without abnormalities; PI, pulmonary insufficiency; TI, tricuspidal insufficiency; TV: tortuous vessels.

[a]Data in a normal range, but accurate value is not available

[b]Ref: males <2.5 mg/mmol, females <3.5 mg/mmol)

[c]Ref: males: 52.2–259.9, females: 12.6–93.9)

reported abdominal pain at baseline, and five had decreasing pain during the study period. One patient had unchanged symptoms, two patients reported increasing symptoms during the follow-up (VAS: 0–1 and 1–3.5).

Level of energy

Mean VAS-scores at baseline, 12 months, 36 months and at last follow-up were in boys: 5.8, 2.0, 1.2, 1.0, respectively, in girls: 7.1, 1.0, 2.3, 0, respectively and in boys and girls combined: 6.3, 1.6, 1.5, 0.8, respectively. Ten of ten patients experienced increased level of energy (Fig. 1).

Headache

The mean number of episodes per month at baseline, 12 months, 36 months and at last follow-up were in boys: 6,5, 0,8, 0,2, 0, respectively, in girls: 13.3, 5.3, 12.7, 3.0, respectively and in boys and girls combined: 9.2, 2.6, 4.9, 1.0, respectively.

Five boys and three girls had frequent headache (up to daily) at baseline. A reduction of number of episodes with headache was seen in seven of eight patients during the follow-up period. One girl had increasing episodes of headache during the follow-up, another girl had no headache at baseline, but developed this during the study. The high number of episodes of headache for girls at 36 months represents the girl developing headache during the study (Fig. 2).

Physical exercise

Mean values of PE [scored from 4 (bad) to 1 (good)] at baseline, 12 months, 36 months and at last follow-up were in boys: 3.2, 1.7, 1.2, 1.5, respectively, in girls: 2.5, 1.5, 1.7, 1.5, respectively and in boys and girls combined: 2.9, 1.6, 1.4, 1.5, respectively.

Nine of ten patients reported increased PE performance compared with baseline when asked how they performed in PE and how their endurance was (Fig. 3).

Safety

Six of ten patients had adverse events related to the infusions within the follow-up period.

Two boys presented with several episodes of chills, headache, nausea and urticaria after respectively 2 and 5 years of treatment with agalsidase-beta. Two girls and one boy developed headache and dizziness in relation to the first agalsidase-beta infusions. The symptoms were well controlled with premedication (non-steroidal anti-inflammatory drugs, antihistamine and/or paracetamol).

One boy had pronounced, recurring stomach-pain in relation to the agalsidase-beta infusion, which disappeared upon switching to agalsidase-alfa (Replagal).

One boy developed after 6 months of treatment, chills, fever, vomiting and tachypnoea one day post-infusion. After several episodes it proved that the symptoms were due to a Port-a-Cath bacterial colonisation with bacteraemia, and symptoms disappeared after removal of the Port-a-Cath.

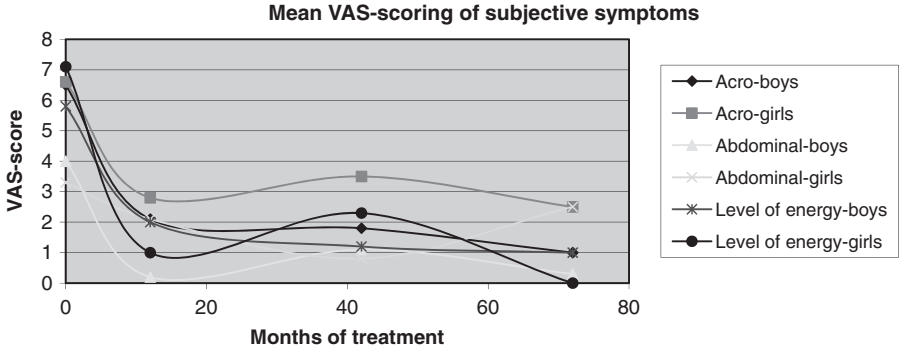

Fig. 1. Mean visual analogue scale (VAS)-scoring of subjective symptoms: acroparaesthesias, abdominal pain and level of energy specified for boys ($N = 6$) and girls ($N = 4$) during the follow-up period. (Acroparaesthesias and abdominal pain, VAS-scoring 0 = no pain, 10 = worst imaginable pain, Level of energy, VAS-scoring 0 = highest level of energy, 10 = lowest level of energy).

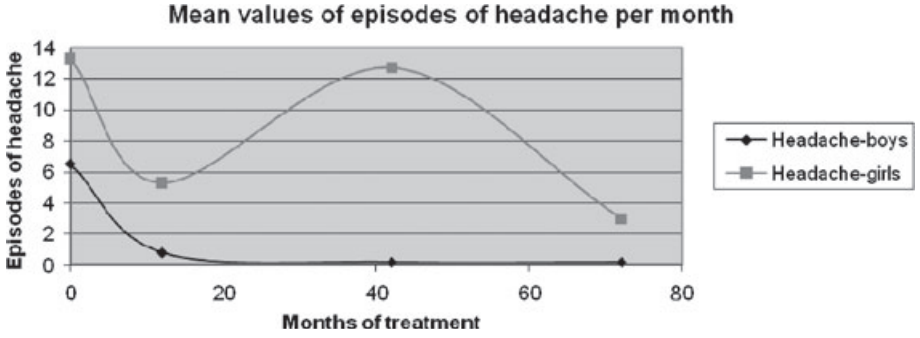

Fig. 2. Mean values of episodes of headache per month specified for boys ($N = 6$) and girls ($N = 4$) during the follow-up period.

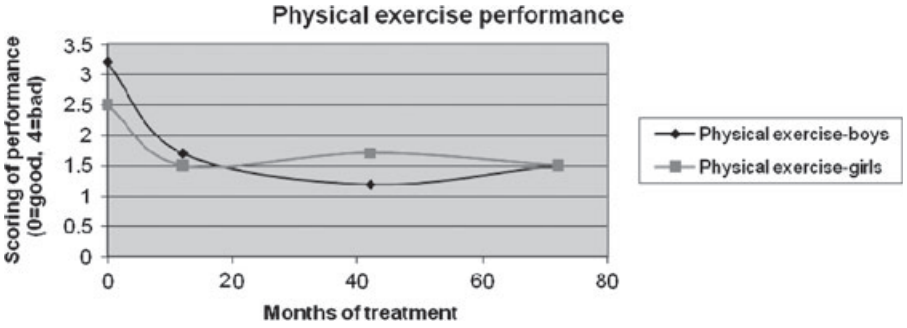

Fig. 3. Mean values of physical exercise performance specified for boys ($N = 6$) and girls ($N = 4$) during the follow-up period.

One patient developed immunoglobulin G antibodies to Fabrazyme after 7 years of treatment.

Discussion

We have studied 10 children and adolescents with Fabry disease up to 8 years after start of ERT. We did not find any of the severe Fabry manifestations from heart, kidney or brain at baseline or during the study. We documented that various types of pain were major symptoms during childhood and adolescence and ERT may ameliorate such pain.

The cardiac complications reported at baseline in this study population were similar to those previously described for untreated patients and demonstrate the progression of cardiac valvular involvement even during childhood (19). Values for left ventricular mass (LVM) were not reported systematically (mostly only reported as 'normal'). For the few patients where values for LVM were given, we did not find a reduction of LVM during the ERT follow-up period corresponding to data by Schiffmann et al. (8).

Kidney disease in Fabry disease may present in late childhood and histological signs of GB_3 accumulation may be evident even earlier (20).

In this study, GFR and albumin and protein/creatinine ratios were normal (including no hyperfiltration) at baseline and throughout the follow-up in essentially all patients corresponding to data from a register-based study of eight children with Fabry by Ramaswami et al. (6).

Tondel et al. (20) did renal biopsies in nine children aged 7–18 years and found podocyte damage in all. Seven of these nine children had microalbuminuria, while GFR were normal in all. All our urine samples were spot-samples, which may have made our measurements less robust than the 24-h or overnight urine collections performed by Tondel et al. (20). If podocyte damage is as frequent in Fabry children as described by Tondel et al. (20), GFR and albumin/creatinine ratio based on urine spot-samples may not be sufficiently sensitive to uncover early renal compromise. However, in young male adults with Fabry, microalbuminuria and reduced GFR is common (21) and the absence of these findings in our adolescents is encouraging. It has been shown that in adult patients with proteinuria above 1 g/24 h at baseline, GFR declined during subsequent ERT, but remained stable in the patients with less proteinuria (20). Thus, the finding of normal protein/albumin excretion in our cohort may possibly indicate that we should be able to maintain normal GFR and that eventual podocyte damage could be reversible or at least not limiting a stabilizing effect of ERT.

Improved sweating capability was found for the majority of the boys in this study. This has been shown previously in studies using agalsidase-alfa (5, 7), but not previously in children given agalsidase-beta. The effect was sustained throughout the observation period in contrast to findings by Schiffmann et al. (8).

Plasma and urine Gb_3 concentrations decreased for the majority of the patients during treatment as also shown by Ramaswami et al. (5), but Gb_3 has not been confirmed as a useful biomarker in clinical trials (1). Globotriaosylsphingosine (Lyso-GB_3) was not measured in this study and may be a better biomarker in Fabry disease (22).

In this study, the most pronounced effect of ERT was a reduction of pain, which was of early onset and sustained in most children throughout the study period. This was evident both for reduction of neuropathic, abdominal pain and headache in most of the children as also shown by other authors in ERT studies using agalsidase-alfa (6, 8, 11), but only limited data were available for agalsidase-beta (10).

Eight children complained of migraine-like headache at baseline and headache may be more common in children with Fabry disease than documented in the literature (23). All experienced disappearance or dramatic improvements of their headache except one girl, who also did not experience reduction of abdominal pain and increase in PE performance during ERT.

Chronic pain is one of the most difficult aspects of Fabry disease, which may have significant, immediate and long-acting impact on physical function, mental health and quality of life. In the opinion of the authors, such modification of the pain phenotype as seen with ERT with sustained reduction in pain during childhood may be very important for how these children perceive themselves and enter adulthood.

Agalsidase-beta was generally well tolerated in children. Only one of the IRR was considered severe: a Port-a-Cath bacterial colonisation with bacteraemia. All of the IRR were managed effectively by premedication.

The frequency of IRR in our cohort was higher than that reported in other studies using agalsidase-beta. In one of the studies 37.5% of the patients experienced IRRs during the study period (10). A shorter follow-up period (48 weeks) may explain the lower frequency of IRRs in that study.

There is no consensus concerning when to start ERT in childhood. Initiation of ERT has been considered reasonable if a child has uncontrolled pain leading to altered lifestyle and reduced quality of life, severe asthenia, lethargy, gastrointestinal symptoms, abnormal MRI findings, episodic vertigo, intraventricular conduction defects, poor growth that cannot be accounted for by another cause. These were also the criteria for starting ERT in the present study. Prevention may be the best reason to start ERT in childhood as some pathological changes over time may become irreversible and refractory to ERT, such as kidney dysfunction (24). However, to show that ERT is preventive, we need longer-term follow-up studies.

The decision whether and when to start ERT is not easy and should be based on many factors of which the good response on chronic pain could be a good reason. Other important factors to consider are the family history (6) and the proposed preventive effect of ERT on future irreversible damage that with this study remains unproven but not improbable. Close monitoring of all children with Fabry disease is important in the opinion of the authors and in the present absence of a clear prognostic clinical and biochemical indicator, initiation of ERT at time of the first symptom of disease in children may be considered to offer best possible treatment and prevention.

Study limitations

The data in this study were retrospectively obtained and were based on review of medical reports and no untreated control group was followed.

As Fabry is a rare disease, the number of patients included in this study are small, which may make our results uncertain and prevent proper statistical analysis.

Acknowledgements

Special thanks to nurse specialist Ea Lilleaas, Centre for Inherited Metabolic Disorders, nurse specialist Ira Hagen, Department of Endocrinology, Department of Ophthalmology, Department of Clinical Physiology, Nuclear Medicine and PET, Department of Growth and Reproduction, Department of Otolaryngology, Head and Neck Surgery, Department of Paediatrics and Adolescent Medicine, Department of Diagnostic Radiology, all at Rigshospitalet, Copenhagen University Hospital, Denmark. Associate Professor, Lis Hasholt, Department of Cellular and Molecular Medicine, Panum Institute, University of Coenhagen, Denmark. Jan-Eric Mansson, Sahlgrenska University Hospital, Sweden; U. F.-R. received a grant from Arvid Nilsson'd Fund.

Ethics approval

This study was approved by the Danish ethic committee, protocol number: H-1-2012-FSP-20.

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