Molecular Genetics and Metabolism 109 (2013) 174–178

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Enzyme replacement therapy and fatigue in adults with Pompe disease

Deniz Güngör [a], Juna M. de Vries [b], Esther Brusse [b], Michelle E. Kruijshaar [a], Wim C.J. Hop [d], Magda Murawska [d], Linda E.M. van den Berg [a], Arnold J.J. Reuser [c], Pieter A. van Doorn [b], Marloes L.C. Hagemans [a], Iris Plug [a], Ans T. van der Ploeg [a,*]

[a] Center for Lysosomal and Metabolic Diseases, Department of Pediatrics, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[b] Center for Lysosomal and Metabolic Diseases, Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[c] Center for Lysosomal and Metabolic Diseases, Department of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[d] Department of Biostatistics, Erasmus MC University Medical Center, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 26 March 2013
Accepted 26 March 2013
Available online 3 April 2013

Keywords:
Pompe disease
Lysosomal storage disorders
Enzyme replacement therapy
Alglucosidase alfa
Fatigue

ABSTRACT

Background: Pompe disease is a hereditary metabolic myopathy, for which enzyme replacement therapy (ERT) has been available since 2006. We investigated whether ERT reduces fatigue in adult patients with Pompe disease.
Methods: In this prospective international observational survey, we used the Fatigue Severity Scale (FSS) to measure fatigue. Repeated measures ANOVA was used to analyze the data over time. In a subgroup of patients, we also evaluated muscle strength using the Medical Research Council Scale, measured pulmonary function as Forced Vital Capacity, and assessed depression using the Hospital Anxiety and Depression Scale.
Results: We followed 163 patients for a median period of 4 years before ERT and for 3 years during ERT. Before ERT, the mean FSS score remained stable at around 5.3 score points; during ERT, scores improved significantly by 0.13 score points per year ($p < 0.001$). Fatigue decreased mainly in women, in older patients and in those with shorter disease duration. Patients' improvements in fatigue were moderately correlated with the effect of ERT on depression (r 0.55; CI 95% 0.07 to 0.70) but not with the effect of ERT on muscle strength or pulmonary function.
Conclusions: Fatigue is a common and disabling problem in patients with early and advanced stages of Pompe disease. Our finding that ERT helps to reduce fatigue is therefore important for this patient population, irrespective of the mechanisms underlying this effect.

1. Introduction

Fatigue accompanies many chronic neuromuscular and neurological disorders [1,2], and is often reported by patients with Pompe disease [3–5], an inherited metabolic myopathy caused by deficiency of acid alpha-glucosidase, a lysosomal enzyme. Pompe disease presents as a wide clinical spectrum, the most prominent symptoms in adults being muscle weakness and respiratory distress [6,7]. As well as these main symptoms, many adults – however badly affected – complain of fatigue [5].

The pathophysiology of fatigue in neurological disorders is not fully understood. As well as physiological changes in the muscle or the Central Nervous System (CNS), it may involve respiratory dysfunction and/or inadequate energy expenditure or energy production. Psychological fatigue ('weariness') may also be involved [1,2,8].

At present there are no proven therapeutic strategies to combat fatigue. Its general management involves identifying and treating contributory factors such as psycho-sociological factors, sleep disturbances, and comorbidities [1].

Since 2006, enzyme replacement therapy (ERT) has become available for Pompe disease. Though this has been shown to positively affect respiratory and muscle functions in adults [9–13], very little is known about its effect on fatigue. While three studies suggested that ERT reduces fatigue in adult patients [14–16], we do not know of any study that has investigated this subject in detail.

To establish whether ERT reduces fatigue, we therefore investigated a large international cohort of adult Pompe patients. We also investigated whether the potential effect of ERT on fatigue differed between subgroups of patients, and whether it was related to improvements or changes in muscle strength, pulmonary function, and/or depression.

Abbreviations: ERT, Enzyme replacement therapy; FSS, Fatigue Severity Scale; MRC, Medical Research Council; FVC, Forced Vital Capacity; HADS, Hospital Anxiety and Depression Scale.

* Corresponding author at: Department of Pediatrics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center — Sophia Children's Hospital, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands. Fax: +31 10 36801.
E-mail addresses: d.gungor@erasmusmc.nl (D. Güngör), j.m.devries@erasmusmc.nl (J.M. de Vries), e.brusse.1@erasmusmc.nl (E. Brusse), m.kruijshaar@erasmusmc.nl (M.E. Kruijshaar), w.hop@erasmusmc.nl (W.C.J. Hop), m.murawska@erasmusmc.nl (M. Murawska), l.vandenberg@erasmusmc.nl (L.E.M. van den Berg), a.reuser@erasmusmc.nl (A.J.J. Reuser), p.a.vandoorn@erasmusmc.nl (P.A. van Doorn), mlc_hagemans@erasmusmc.nl (M.L.C. Hagemans), i.plug@erasmusmc.nl (I. Plug), a.vanderploeg@erasmusmc.nl (A.T. van der Ploeg).

1096-7192/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ymgme.2013.03.016

2. Material and methods

2.1. Patients and settings

Data were collected between May 2002 and February 2011 as part of an ongoing observational follow-up study on the clinical course of Pompe disease in patients in Australia, Canada, Germany, The Netherlands, United States, United Kingdom, and in a small number of patients from other countries. Patients were recruited through national patient organizations or directly through our expertise center, the Center for Lysosomal and Metabolic Diseases at Erasmus MC University Medical Center, as described previously [3,5]. The study was approved by the Erasmus MC Ethical Committee, and all participants provided written informed consent.

Beyond a diagnosis of Pompe disease, there were no strict inclusion or exclusion criteria for participation in the study. For the analyses described in this paper, we included only patients aged 18 years and older who were receiving ERT, and who had had at least 6 months of follow-up before and after ERT.

2.2. Measurements

Each year, participants were asked to complete several questionnaires, including one on fatigue. Demographic and clinical data were collected on country of residence, age, year of diagnosis, gender, disease duration, and use of wheelchair and/or ventilator.

For patients seen at the Dutch center, more frequent measurements and additional data were available from clinical assessments and further questionnaires. As well as fatigue, these included pulmonary function and muscle strength (assessed between January 2005 and August 2009) and depression (assessed between January 2005 and February 2011) measured as described below.

2.2.1. Fatigue assessment

The severity and impact of fatigue were assessed using the Fatigue Severity Scale (FSS) [17]. This self-report questionnaire focuses on the physical symptoms of fatigue, and measures the severity of fatigue and its impact on an individual's daily functioning. A mean score is calculated from the nine items, which range from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Scores $\geq$4 indicate the presence of fatigue, and scores $\geq$5 severe fatigue [17,18]. As described previously [5], we used the English, Dutch and German translations. The FSS has demonstrated good internal consistency, reliability and validity in studies involving patients with several neurological disorders [5,17,19,20]. When individual item scores were missing, the mean FSS score was calculated from the remaining items [5]. The maximum number of missing items per questionnaire was 2, and missing items were found in only 2% of the 1199 questionnaires completed.

2.2.2. Pulmonary function (Dutch patients)

Forced Vital Capacity (FVC) in sitting and supine positions was measured using spirometry as described previously [21]. Results were expressed as a percentage of the predicted normal value.

2.2.3. Muscle strength (Dutch patients)

Skeletal muscle strength was measured manually in scores from 0 to 5 using the Medical Research Council (MRC) grading scale [22]. A sum score was calculated by adding the grades of 26 muscle groups as described earlier [23]. This sum score could range from 0 (total paralysis) to 130 (normal strength), and was expressed as a percentage of the maximum possible score of 130. When 3 or more muscle groups were missing, the score was not calculated [23].

2.2.4. Depression (Dutch patients)

Symptoms of depression were assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) [24], which ranges from 0 to 21.The HADS has been widely used in different disorders (including neuromuscular disorders), and has demonstrated good reliability and validity [25].

2.3. Statistical analysis

Analyses of the longitudinally assessed fatigue scores were performed using repeated measures ANOVA (random coefficient models), which allows for irregular measurement times. To assess the effect of ERT on the mean FSS scores, the model included linear effects of time before ERT and time after ERT. Per individual, the two segments connect at the time ERT started, a method generally known as the "broken-stick" method or "piece-wise linear regression". The two regression coefficients provide estimates of the mean annual change (slope) of the scores before and after the start of ERT. The difference between these two provides an estimate of the effect of ERT on the outcome measure.

For subgroup analyses, patients were divided into strata based on gender, age, disease duration, wheelchair use, and use of respiratory support, all at start of ERT.

For the Dutch patients we also analyzed the correlation between the effect of ERT on the FSS and its effect on the MRC sum score, on FVC in upright and supine positions, and on the HADS depression score. After performing univariate analysis by using linear mixed-effects models with broken-stick evolutions for the FSS and the three other outcomes, we estimated random effects for each model using empirical Bayes estimates (EB). Afterwards the correlation between the EB estimates for FSS and the other outcomes was calculated. The significance of the correlation coefficients was tested using 95% confidence intervals obtained from 1000 bootstrap samples.

Data were analyzed using SPSS for Windows (version 17, SPSS Inc., Chicago, IL) and SAS (version 9.2, SAS Institute Inc., Cary, NC). Bootstrap sampling was implemented in R (version 2.14). A p-value of $\leq$0.05 was considered statistically significant.

3. Results

3.1. General characteristics

The eligibility criteria were met by 163 adults (55% female) out of a total of 383 patients participating in the survey. Thirty patients were excluded as they were younger than 18 years of age, 67 were excluded for not receiving ERT, 85 had no follow-up measurements (yet), and 38 had less than 6 months follow-up before and/or after the start of ERT.

The 163 patients in our study (see Table 1) had a median disease duration of 13 years. The patients' median age at start of ERT was 50 years (range 24–76 years); 52% used a wheelchair and 50% respiratory support. The median follow-up time before ERT was 4 years (range 0.5–8); after start of ERT, this was 3 years (range 0.5–8). Per patient, a median of seven questionnaires were completed (range 2–18).

At start of ERT, 85% of the patients with an available FSS score were fatigued (FSS $\geq$ 4) and 68% severely fatigued (FSS $\geq$ 5); at the last measurement, 79% were fatigued and 55% severely fatigued.

3.2. Change in fatigue scores before and during ERT

Before ERT, the mean FSS score remained stable (annual change of 0.01 score points; CI 95% −0.05 to 0.06; $p = 0.84$). In contrast, the mean fatigue score declined significantly during ERT by 0.13 score points per year (CI 95% −0.19 to −0.07; $p < 0.001$). Comparison of the trends in fatigue over time in the periods before and after the start of ERT showed that fatigue significantly improved during ERT (mean difference in slopes 0.14 FSS score points per year, 95% CI −0.23 to −0.04; $p < 0.01$, Fig. 1).

Relative to fatigue in the pre-treatment period, fatigue during ERT improved significantly in women, in older patients and in those whose disease duration was <15 years. This improvement was not statistically significant in men, younger patients, and those with longer

Table 1
Patient characteristics at start of ERT.

Characteristic	All (n = 163)
Median age at start of ERT, years (range)	50 (24–76)
Median age at diagnosis, years (range)	37 (1–66)
Median disease duration, years (range)	13 (1–33)
Gender, no. (%)	
Female	90 (55)
Country of residence, no. (%)	
The Netherlands	59 (36)
Germany	36 (22)
US	37 (23)
Other[a]	31 (19)
Use of wheelchair at start of ERT, no. (%)	
Yes	85 (52)
Respiratory support at start of ERT[b], no. (%)	
Yes	81 (50)

Continuous variables are expressed as median (range). Categorical variables are expressed as numbers (%).
[a] Includes patients from Australia, Canada, United Kingdom and a small number of patients from other countries.
[b] Respiratory support includes partial and fulltime, invasive and non-invasive support.

disease duration (Table 2). Fatigue improved significantly in patients who used a wheelchair and in those who were not on respiratory support. It also tended to improve in wheelchair-independent patients ($p = 0.06$) and in those who received any kind of respiratory support ($p = 0.08$). Statistical testing of the differences between these subgroups showed that these differences were not significant for any of the aforementioned subgroups.

3.3. Correlation between the effect of ERT on fatigue and its effect on muscle strength, pulmonary function and depression

For this part of the analysis, only the 59 Dutch patients were included. At start of ERT, their median age was 52 years (range 26–76), 59% were women and 46% used a wheelchair. Relative to the total study population, fewer patients used respiratory support (32% versus 50%) and more were fatigued at start of ERT (92% versus 85% of the total patient population). Median MRC sum score (in percentage) at start of ERT was 78% (range 48–92). Median FVC percentages were 70% in sitting position (range 11–107) and 49% in supine position (range 23–99). Only 13 patients (22%) scored ≥8 on the HADS depression subscale, indicating clinical signs of (borderline) depression. Median HADS depression score was 4 (range 0–15).

As in the total study population, FSS scores significantly decreased during ERT. The difference with the pre-treatment period was borderline significant (Table 3), and was moderately correlated with a decrease in the level of depression (r 0.55; CI 95% 0.07 to 0.70). No significant correlations were found between the improvement in fatigue and muscle strength in response to ERT and in pulmonary function in upright and supine positions.

4. Discussion

This is the first prospective follow-up study to assess the effect of ERT on fatigue in a large number of adult Pompe patients. We found that ERT significantly reduces self-reported fatigue, the mean decrease in FSS score being 0.14 per year relative to the pre-treatment period. The decrease in fatigue during ERT was correlated with improvements in depression, but not significantly with changes in muscle strength or pulmonary function. The effect of ERT on fatigue was not consistent across patient subgroups: fatigue decreased mainly in women, older patients and those with shorter disease duration.

Our study mirrors previous findings in this cohort, providing a reminder that fatigue is a highly prevalent symptom among adults with Pompe disease. Therapies that can reduce fatigue in this population are therefore of great importance, and our finding that ERT positively affects fatigue is a significant finding. While the annual improvement might seem small (0.14 points per year), it resulted in a substantial drop in the proportion of patients who were fatigued or severely fatigued at the end of our follow-up.

Subgroup analyses suggest that fatigue may be more responsive to ERT in women, older patients and those with shorter disease duration. A better response in women might be explained by the more pronounced effect of ERT on muscle strength in females that was identified recently by our group [23]. It is unknown whether hormonal influences are involved in this. The better effect in patients with shorter disease duration might be due to less severe muscle damage. The absence of an effect in younger patients may seem at odds with this, but it is possible

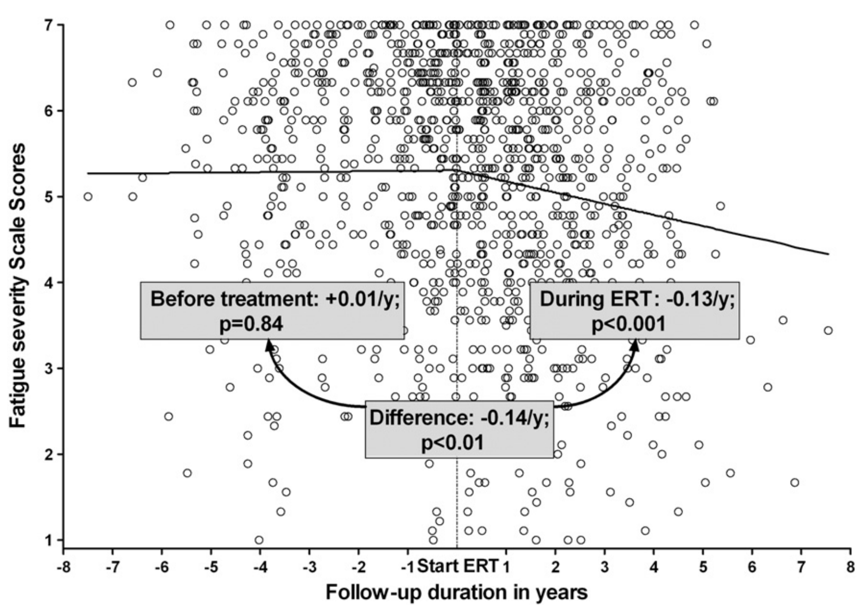

Fig. 1. The figure shows the change in Fatigue Severity-Scale scores (FSS) before and after the start of enzyme replacement therapy (ERT). The dots represent individual measurements and the lines represent the mean slopes calculated by the 'broken stick' repeated measures ANOVA for the group of 163 patients. The median follow-up during the natural course of Pompe disease was 4 years and the median follow-up during treatment was 3 years. The mean FSS score did not change significantly in the period before ERT, but declined significantly during ERT. The difference between the period before and during ERT was 0.14 FSS score points per year ($p < 0.01$).

Table 2
Subgroup analyses for the effect of ERT on the fatigue severity-scale scores.

Subgroups	Difference in FSS score before and during ERT (Comparison between change over time in FSS before and during ERT) Score points/year (95% CI)	p-Value[a]
All	−0.14 (−0.23 to −0.04)	<0.01
Gender		
Female (n = 90)	−0.18 (−0.31 to −0.05)	<0.01
Male (n = 73)	−0.08 (−0.23 to 0.07)	0.30
Age at ERT, years		
<45 (n = 66)	−0.10 (−0.27 to 0.07)	0.26
≥45 (n = 97)	−0.15 (−0.27 to −0.03)	0.01
Disease duration, years		
<15 (n = 94)	−0.19 (−0.32 to −0.05)	<0.01
≥15 (n = 68)	−0.07 (−0.22 to 0.07)	0.33
Wheelchair use		
Yes (n = 85)	−0.13 (−0.24 to −0.01)	0.04
No (n = 78)	−0.15 (−0.32 to 0.01)	0.06
Respiratory support[b]		
Yes (n = 81)	−0.13 (−0.27 to 0.02)	0.08
No (n = 82)	−0.14 (−0.27 to −0.004)	0.04

Data show the mean changes in score points per year (sp/y) as calculated by stratified analysis using repeated measures ANOVA; CI = confidence interval; FSS = Fatigue Severity Scale.
[a] p-Value for the difference in FSS score before and during ERT per subgroup. Statistical testing of the differences between these subgroups showed that these differences were not significant.
[b] Respiratory support includes partial and fulltime, invasive and non-invasive support.

that younger patients have more demanding lifestyles, resulting in more fatigue. Since glycogen degradation occurs mainly in the cytoplasm, we doubt that lower levels of fatigue can be attributed to the increased release of glucose from the lysosome (by ERT mediated lysosomal glycogen degradation) [26].

Muscle strength, pulmonary function and depression, have been shown to be related to fatigue in other neurological disorders [1,2,8]. Against our expectations, we found no significant correlation between the improvement in fatigue and in muscle strength or pulmonary function. This might be due to the smaller sample size available for this sub-analysis. Alternatively, it may be that the level of fatigue is determined by the degree of muscle endurance rather than of muscle strength [27]. Because patients with impaired pulmonary function often use mechanical ventilation, their oxygen levels will be normal, which could explain the absence of a correlation between the response to ERT in fatigue and pulmonary function.

We found that as fatigue decreased during ERT, the scores on the depression scale also decreased. Several studies have described a relationship between depression and fatigue in neurological disorders [2,28–31]. Depression may predispose for fatigue [2,28], but fatigue secondary to an underlying illness can also cause depression, with one sometimes influencing the other [29]. Since the majority of patients (78%) were not depressed, ERT has presumably contributed to a decrease in fatigue by affecting the underlying pathophysiology.

As fatigue is a multifactorial entity, it is likely that other factors – including changing patient's perspectives and perceptions, intensified medical care and altered muscle metabolism – contribute to its improvement after ERT. Although, as a treatment of the underlying disease, ERT seemed to reduce fatigue, it is hard to define the extent to which it acts directly (by reversing disease-related pathophysiology) or indirectly (through psycho-sociological factors). Further research is needed to unravel the underlying mechanisms.

This study benefits from the relatively large number of patients who participated, and from the fact that patients were included irrespective of their disease severity; the study thereby represents the entire spectrum of adult Pompe disease. Despite the large sample, it was not possible to build multivariate models, and multiple testing might limit the results of the subgroup analysis. Our correlation analysis was based on a subset of patients and was limited by a smaller sample size.

Fatigue is a subjective and complex concept that is difficult to define and measure. The FSS is a uni-dimensional scale that measures fatigue as a single construct. Because of its brevity and simplicity, we preferred the FSS to a multi-dimensional scale in which different forms of fatigue – such as physical, cognitive and psychosocial fatigue – are assessed separately. Uni-dimensional and multi-dimensional scales have been found to produce similar measurements of fatigue [32].

5. Conclusions

Fatigue is a common problem in patients with Pompe disease. Our finding that ERT helps to reduce it is therefore important for this patient population, irrespective of the mechanisms underlying this effect. Fatigue decreased mainly in women, in older patients and in patients with short disease duration.

To manage fatigue successfully, treatment options such as rehabilitation and exercise [33] should be considered in addition to ERT. Further investigations should be devoted to the roles of pharmacotherapeutics and cognitive therapy in treating fatigue, and to the exact role of muscle cell changes, pulmonary function, and psychological and other factors that may be associated with it.

Conflicts of interest and funding

Research on Pompe disease at Erasmus MC is financially supported by the following parties: ZonMw — The Netherlands Organisation for Health Research and Development [project no. 152001005]; the Dutch TI Pharma initiative “Sustainable Orphan Drug Development through Registries and Monitoring (T6-208)”; “EUCLYD — a European Consortium for Lysosomal Storage Diseases” (health F2/2008 grant agreement

Table 3
Change in fatigue as a result of ERT and its correlation with the change over time in muscle strength, pulmonary function and level of depression.

	Change over time		Difference before and after ERT	Correlation to FSS[a]
	Before ERT (95% CI)	During ERT (95% CI)	(95% CI)	r (95% CI)
Main outcome measure				
FSS (n = 59)	−0.04 (−0.13 to 0.04)	−0.21 (−0.33 to −0.09)[b]	−0.17 (−0.35 to 0.01)	Reference
Covariates				
MRC sum score (n = 55[c])	−1.28 (−1.80 to −0.49)[b]	2.01 (1.20 to 2.81)[b]	3.29 (2.04 to 4.53)[b]	−0.36 (−0.61 to 0.08)
FVC upright position (n = 52[c])	−1.95 (−3.09 to −0.83)[b]	0.06 (−1.09 to 1.21)	2.02 (0.26 to 3.77)[b]	−0.26 (−0.49 to 0.08)
FVC supine position (n = 45[c])	−1.71 (−2.76 to −0.67)[b]	−0.67 (−1.79 to 0.45)	1.04 (−0.50 to 2.57)	−0.31 (−0.56 to 0.17)
HADS depression (n = 59[c])	0.08 (−0.40 to 0.48)	−0.48 (−0.85 to −0.11)[b]	−0.57 (−1.23 to 0.09)	0.55 (0.07 to 0.70) [b]

Data show the mean changes in score points per year (sp/y) as calculated by univariate analysis using linearnmixed-effects models; C-I = confidence interval; FSS = Fatigue Severity Scale; MRC = Medical Research Council; FVC = Forced Vital Capacity; HADS = Hospital Anxiety Depression Scale.
[a] Correlation between the differences in FSS scores and the difference in the other outcome measures following ERT.
[b] Represents statistical significance.
[c] Only patients with sufficient data were included.

201678); the Prinses Beatrix Fonds [project no. OP07-08]; and Genzyme Corporation, Cambridge, MA, USA. Since August 2004, A.T. van der Ploeg, MD, PhD and A.J.J. Reuser, PhD, have provided consulting services for Genzyme Corp, Cambridge, MA, USA, under an agreement between Genzyme Corporation and Erasmus MC, Rotterdam, The Netherlands. This agreement also covers financial support for Erasmus MC to pursue research in the field of Pompe disease. Erasmus MC and inventors of the method of treatment of Pompe disease by enzyme replacement therapy receive royalty payments pursuant to Erasmus MC policy on nventions, patents and technology transfer. D. Güngör, MD, J.M. de Vries, MD, E. Brusse, MD, PhD, M.E. Kruijshaar, PhD, W.C.J. Hop, PhD, M. Murawska, MS, L.E.M. van den Berg, MD, P.A. van Doorn, MD, PhD, M.L.C. Hagemans, PhD, and I. Plug, PhD report no disclosures. Funders of the study had no role in design and conduct of the study, data collection, data management, data analysis, data interpretation, or preparation, review, or approval of the manuscript. The principal authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and all authors made the decision to submit for publication.

Acknowledgments

This study was a joint initiative of the International Pompe Association (IPA) and Erasmus MC University Medical Center (Erasmus MC). We thank all patients for participating in the study and Ria Broekgaarden, the Family House, Allan Muir, Thomas Schaller, Guy Ashford-Smith, Helen Walker, Marsha Zimmerman and Rineke Nelisse for their contribution to the organizational part of the study. We thank David Alexander for his critical reading of the manuscript, and would like to acknowledge Dimitris Rizopoulos from the Department of Biostatistics at Erasmus MC for his statistical advice.

References

[1] J.M. de Vries, M.L. Hagemans, J.B. Bussmann, A.T. van der Ploeg, P.A. van Doorn, Fatigue in neuromuscular disorders: focus on Guillain–Barre syndrome and Pompe disease, Cell Mol. Life Sci. 67 (2010) 701–713.
[2] A. Chaudhuri, P.O. Behan, Fatigue in neurological disorders, Lancet 363 (2004) 978–988.
[3] M.L. Hagemans, L.P. Winkel, P.A. Van Doorn, W.J. Hop, M.C. Loonen, A.J. Reuser, A.T. Van der Ploeg, Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients, Brain 128 (2005) 671–677.
[4] L.E. van den Berg, J.M. de Vries, R.M. Verdijk, A.T. van der Ploeg, A.J. Reuser, P.A. van Doorn, A case of adult Pompe disease presenting with severe fatigue and selective involvement of type 1 muscle fibers, Neuromuscul. Disord. 21 (2011) 232–234.
[5] M.L. Hagemans, S.P. van Schie, A.C. Janssens, P.A. van Doorn, A.J. Reuser, A.T. van der Ploeg, Fatigue: an important feature of late-onset Pompe disease, J. Neurol. 254 (2007) 941–945.
[6] A.T. van der Ploeg, A.J. Reuser, Pompe's disease, Lancet 372 (2008) 1342–1353.
[7] A. Engel, R. Hirschhorn, M.L. Huie, Acid maltase deficiency, in: A. Engel, C. Franzini-Armstrong (Eds.), Myology, McGraw-Hill, New York, 2004.
[8] U. Mellies, F. Stehling, C. Dohna-Schwake, R. Ragette, H. Teschler, T. Voit, Respiratory failure in Pompe disease: treatment with noninvasive ventilation, Neurology 64 (2005) 1465–1467.
[9] A.T. van der Ploeg, P.R. Clemens, D. Corzo, D.M. Escolar, J. Florence, G.J. Groeneveld, S. Herson, P.S. Kishnani, P. Laforet, S.L. Lake, D.J. Lange, R.T. Leshner, J.E. Mayhew, C. Morgan, K. Nozaki, D.J. Park, A. Pestronk, B. Rosenbloom, A. Skrinar, C.I. van Capelle, N.A. van der Beek, M. Wasserstein, S.A. Zivkovic, A randomized study of alglucosidase alfa in late-onset Pompe's disease, N. Engl. J. Med. 362 (2010) 1396–1406.
[10] C. Angelini, C. Semplicini, S. Ravaglia, B. Bembi, S. Servidei, E. Pegoraro, M. Moggio, M. Filosto, E. Sette, G. Crescimanno, P. Tonin, R. Parini, L. Morandi, G. Marrosu, G. Greco, O. Musumeci, G. Di Iorio, G. Siciliano, M.A. Donati, F. Carubbi, M. Ermani, T. Mongini, A. Toscano, G.G. Italian, Observational clinical study in juvenile–adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years, J. Neurol. 259 (2012) 952–958.
[11] S. Strothotte, N. Strigl-Pill, B. Grunert, C. Kornblum, K. Eger, C. Wessig, M. Deschauer, F. Breunig, F.X. Glocker, S. Vielhaber, A. Brejova, M. Hilz, K. Reiners, W. Muller-Felber, E. Mengel, M. Spranger, B. Schoser, Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial, J. Neurol. 257 (2010) 91–97.
[12] B. Bembi, F.E. Pisa, M. Confalonieri, G. Ciana, A. Fiumara, R. Parini, M. Rigoldi, A. Moglia, A. Costa, A. Carlucci, C. Danesino, M.G. Pittis, A. Dardis, S. Ravaglia, Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II, J. Inherit. Metab. Dis. 33 (2010) 727–735.
[13] A. Toscano, B. Schoser, Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review, J. Neurol. 260 (2013) 951–959.
[14] C.I. van Capelle, L.P. Winkel, M.L. Hagemans, S.K. Shapira, W.F. Arts, P.A. van Doorn, W.C. Hop, A.J. Reuser, A.T. van der Ploeg, Eight years experience with enzyme replacement therapy in two children and one adult with Pompe disease, Neuromuscul. Disord. 18 (2008) 447–452.
[15] G.K. Papadimas, K. Spengos, A. Konstantinopoulou, S. Vassilopoulou, A. Vontzalidis, C. Papadopoulos, H. Michelakakis, P. Manta, Adult Pompe disease: clinical manifestations and outcome of the first Greek patients receiving enzyme replacement therapy, Clin. Neurol. Neurosurg. 113 (2011) 303–307.
[16] D. Orlikowski, N. Pellegrini, H. Prigent, P. Laforet, R. Carlier, P. Carlier, B. Eymard, F. Lofaso, D. Annane, Recombinant human acid alpha-glucosidase (rhGAA) in adult patients with severe respiratory failure due to Pompe disease, Neuromuscul. Disord. 21 (2011) 477–482.
[17] L.B. Krupp, N.G. LaRocca, J. Muir-Nash, A.D. Steinberg, The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus, Arch. Neurol. 46 (1989) 1121–1123.
[18] I.S. Merkies, P.I. Schmitz, J.P. Samijn, F.G. van der Meche, P.A. van Doorn, Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group, Neurology 53 (1999) 1648–1654.
[19] A.J. Dittner, S.C. Wessely, R.G. Brown, The assessment of fatigue: a practical guide for clinicians and researchers, J. Psychosom. Res. 56 (2004) 157–170.
[20] M.P. Garssen, R. Van Koningsveld, P.A. Van Doorn, Residual fatigue is independent of antecedent events and disease severity in Guillain–Barre syndrome, J. Neurol. 253 (2006) 1143–1146.
[21] N.A. van der Beek, C.I. van Capelle, K.I. van der Velden-van Etten, W.C. Hop, B. van den Berg, A.J. Reuser, P.A. van Doorn, A.T. van der Ploeg, H. Stam, Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease, Mol. Genet. Metab. 104 (2011) 129–136.
[22] Medical Research Council, Aids to Examination of the Peripheral Nervous System, Her Majesty's Stationary Office, London, 1976.
[23] J.M. de Vries, N.A. van der Beek, W.C. Hop, F.P. Karstens, J.H. Wokke, M. de Visser, B.G. van Engelen, J.B. Kuks, A.J. van der Kooi, N.C. Notermans, C.G. Faber, J.J. Verschuuren, M.E. Kruijshaar, A.J. Reuser, P.A. van Doorn, A.T. van der Ploeg, Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study, Orphanet J. Rare Dis. 7 (2012) 73.
[24] Snaith Zigmond, The Hospital Anxiety and Depression Scale, Acta Psychiatr. Scand. (1983) 361–370.
[25] I. Bjelland, A.A. Dahl, T.T. Haug, D. Neckelmann, The validity of the Hospital Anxiety and Depression Scale. An updated literature review, J. Psychosom. Res. 52 (2002) 69–77.
[26] N. Preisler, P. Laforet, K.L. Madsen, R.S. Hansen, Z. Lukacs, M.C. Orngreen, A. Lacour, J. Vissing, Fat and carbohydrate metabolism during exercise in late-onset Pompe disease, Mol. Genet. Metab. 107 (2012) 462–468.
[27] W. McArdle, Skeletal muscle: structure and function, in: D. Balado (Ed.), Exercise Physiology, Williams and Wilkins, Baltimore, 1996, pp. 314–336.
[28] L.B. Strober, P.A. Arnett, An examination of four models predicting fatigue in multiple sclerosis, Arch. Clin. Neuropsychol. 20 (2005) 631–646.
[29] P. Skapinakis, G. Lewis, V. Mavreas, Temporal relations between unexplained fatigue and depression: longitudinal data from an international study in primary care, Psychosom. Med. 66 (2004) 330–335.
[30] E. Brusse, M.G. Brusse-Keizer, H.J. Duivenvoorden, J.C. van Swieten, Fatigue in spinocerebellar ataxia: patient self-assessment of an early and disabling symptom, Neurology 76 (2011) 953–959.
[31] R.J. Siegert, D.A. Abernethy, Depression in multiple sclerosis: a review, J. Neurol. Neurosurg. Psychiatry 76 (2005) 469–475.
[32] M.P. Garssen, P.I. Schmitz, I.S. Merkies, B.C. Jacobs, F.G. van der Meche, P.A. van Doorn, Amantadine for treatment of fatigue in Guillain–Barre syndrome: a randomised, double blind, placebo controlled, crossover trial, J. Neurol. Neurosurg. Psychiatry 77 (2006) 61–65.
[33] J.B. Bussmann, M.P. Garssen, P.A. van Doorn, H.J. Stam, Analysing the favourable effects of physical exercise: relationships between physical fitness, fatigue and functioning in Guillain–Barre syndrome and chronic inflammatory demyelinating polyneuropathy, J. Rehabil. Med. 39 (2007) 121–125.