Enzyme replacement therapy and fatigue in adults with Pompe disease

Deniz Güngör a, Juna M. de Vries b, Esther Brusse b, Michelle E. Kruijshhaar a, Wim C.J. Hop d, Magda Muraw ska 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,⁎

⁎ Corresponding author at: Department of Pediatrics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center Rotterdam, The Netherlands.

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A B S T R A C T

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.

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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.
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 ≥4 indicate the presence of fatigue, and scores ≥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 ≤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 ≥ 4) and 68% severely fatigued (FSS ≥ 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 disease duration. 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 disease duration.
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

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at start of ERT, years</td>
<td>50 (24–76)</td>
</tr>
<tr>
<td>Median age at diagnosis, years</td>
<td>37 (1–66)</td>
</tr>
<tr>
<td>Median disease duration, years</td>
<td>13 (1–33)</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>90 (55)</td>
</tr>
<tr>
<td>Country of residence, no. (%)</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>59 (36)</td>
</tr>
<tr>
<td>Germany</td>
<td>36 (22)</td>
</tr>
<tr>
<td>US</td>
<td>37 (23)</td>
</tr>
<tr>
<td>Othera</td>
<td>31 (19)</td>
</tr>
<tr>
<td>Use of wheelchair at start of ERT,</td>
<td></td>
</tr>
<tr>
<td>no. (%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Respiratory support at start of ERTb, no. (%)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

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.

![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).](image-url)
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.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Difference in FSS score before and during ERT (Score points/year (95% CI))</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>−0.14 (−0.23 to −0.04)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 90)</td>
<td>−0.18 (−0.31 to −0.05)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male (n = 73)</td>
<td>−0.08 (−0.23 to 0.07)</td>
<td>0.30</td>
</tr>
<tr>
<td>Age at ERT, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 (n = 66)</td>
<td>−0.10 (−0.27 to 0.07)</td>
<td>0.26</td>
</tr>
<tr>
<td>≥45 (n = 97)</td>
<td>−0.15 (−0.27 to −0.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 (n = 94)</td>
<td>−0.19 (−0.32 to −0.05)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥15 (n = 68)</td>
<td>−0.07 (−0.22 to 0.07)</td>
<td>0.33</td>
</tr>
<tr>
<td>Wheelchair use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 85)</td>
<td>−0.13 (−0.24 to −0.01)</td>
<td>0.04</td>
</tr>
<tr>
<td>No (n = 78)</td>
<td>−0.15 (−0.32 to 0.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Respiratory supportb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 81)</td>
<td>−0.13 (−0.27 to 0.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>No (n = 82)</td>
<td>−0.14 (−0.27 to −0.004)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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.

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

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