L-Alanine supplementation in Pompe Disease: a potential therapeutic implementation for patients on ERT?

**A case report**

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**BACKGROUND**

Pompe disease (PD), or glycogen storage disorder type II (GSD II; OMIM 232300), is an inherited lysosomal disorder due to the deficiency of the acid a-glucosidase enzyme (GAA, EC 3.2.1.20) causing multisystemic glycogen accumulation and leading to variable associated phenotypes [1]. Enzyme-replacement therapy (ERT) is currently the main treatment available for patients, highly reverting cardiac muscle involvement and extending life expectancy in infantile patients while still lacking in treating residual symptoms, e.g. skeletal muscle involvement [2]. Before ERT, many other potential treatment strategies have been attempted, such as dietary interventions and oral supplementations [3,4,5,6]. Among those tried, L-alanine supplementation has been shown to reduce protein degradation and muscle breakdown, being a gluconeogenic amino acid capable of decreasing branched-chain AA catabolism even with relatively short period treatment-trials [7].

**SUBJECT**

F. is a 9 y.o. PD female ERT-treated since age 1. Despite early beginning of ERT, F. is developing slowly progressive myopathy conditioning walking difficulties, moderate respiratory impairment and oropharyngeal dysphagia.

**METHODS AND ASSESSMENT.**

This is the first case we report in this open-label study designed for testing possible positive effects of L-alanine oral supplementation (LAOS) during ERT. L-alanine was administered as powder, mixed into a drink or creamy food (mainly milk or yogurt), starting at age 8 yo and 6 mo, with a starting dose of 0.5 g/kg/day TTD for a total of 15g/day. Dosage was maintained unchanged for 6 months total (T1), then increased to 0.6 g/kg/day (total 18g/day) for other 3 months (T2, 9 months after LAOS start).

The following parameters were evaluated at baseline (T0), at 6 (T1) and 9 months (T2):

- **Anthropometric measures** and relative z-scores generated using the WHO 2007 growth charts [8].
- **Body composition** using air displacement plethysmography (BOD-POD\(^\circ\)), providing fat mass (FM), fat free mass (FFM) and relative percentages according to McCarthy 2006 percentiles [9].
- **Indirect calorimetry** (Q-NRG, Cosmed\(^\circ\)) to measure resting energy expenditure (REE) under standardized conditions.
- **3-days-food dietary record**, the patient was requested not to change dietary habits or exercise pattern throughout the study.
- **Biochemical examinations** (Plasma alanine levels, alanine/lysine ratio, muscle enzymes, renal function, transthyretin and albumin).
RESULTS.

At baseline, F’s weight, height and BMI were within normal ranges, while BC demonstrated low FM (<2°pc) and high REE levels (1265 Kcal/day vs. predicted WHO rates = 1133 Kcal/day). A 3-days-food dietary record analysis confirmed a diet higher in proteins (≥ 3.0 g/kg/day), corresponding to 20-25% of total daily energy intakes. This remained unchanged throughout study period and still ongoing. During the study period, the patient was compliant with LAOS treatment protocol and could complete all assessments due; no complications occurred. A progressive FM increase could be observed over the study period (Table 1) and REE, remarkably high at baseline, significantly decreased with a variation of -10% at T2, meaning a reduction of 5.4-8% compared to prediction (Figure 1). Changes in biochemical indices were unremarkable over study period and indices of muscle damage remained substantially unchanged. No increases above considered normal values in Alanine blood concentrations could be observed during study period. On a patient’s perspective, even if difficult to objectify, it’s good to report that F is now reducing the need of walking supports and can now sleep without any pillows.

Table 1. Anthropometric measures and indices of body composition before and during LAOS.

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>28.3</td>
<td>29.4</td>
<td>30.5</td>
</tr>
<tr>
<td>Weight z-score (SD)</td>
<td>0.36</td>
<td>0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>137.2</td>
<td>139.7</td>
<td>141.4</td>
</tr>
<tr>
<td>Height z-score (SD)</td>
<td>1.27</td>
<td>1.03</td>
<td>1.03</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.0</td>
<td>15.1</td>
<td>15.2</td>
</tr>
<tr>
<td>BMI z-score (SD)</td>
<td>-0.49</td>
<td>-0.62</td>
<td>-0.58</td>
</tr>
<tr>
<td>FM %</td>
<td>9.9</td>
<td>11.6</td>
<td>13.4</td>
</tr>
<tr>
<td>FFM %</td>
<td>90.1</td>
<td>88.4</td>
<td>86.6</td>
</tr>
<tr>
<td>FFM Kg</td>
<td>2.8</td>
<td>3.4</td>
<td>4.1</td>
</tr>
<tr>
<td>FFM Kg</td>
<td>25.5</td>
<td>26.0</td>
<td>26.4</td>
</tr>
</tbody>
</table>

T0: baseline pre-LAOS; T1: after 6 months of LAOS; T2: after 3 months of LAOS. Notes: §WHO 2007 Growth Charts.

Figure 1. REE parameters analysis obtained from indirect calorimetry (IC) compared to prediction with most commonly used equations.

CONCLUSION

ERT is not curative for PD patients thus additional treatments should be considered to improve outcomes. Our patient showed physical signs of inability to accumulate energy when exclusively on ERT, while FM increase and REE reduction were demonstrated when supplemented with LAOS, likely reflecting anabolic pathways’ implementation. This is the first case reporting potential LAOS benefits in PD-on ERT patients. Further studies are needed to better understand possible clinical/functional implications, also on the long-term, but our results suggest LAOS as a possible co-treatment strategy.

REFERENCES