Real-world challenges in the management of pediatric Pompe disease: Nutrition, motor function and family burden

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Abstract. Infantile-onset Pompe disease (IOPD) is a severe neuromuscular disorder requiring lifelong multidisciplinary care. The present study aimed to assess nutritional practices, gross motor development and socio-economic burdens in children with IOPD. For this purpose, a cross-sectional study was conducted on children with IOPD receiving enzyme replacement therapy (ERT). Data were obtained from medical records, 24-h dietary recall and caregiver interviews. The median energy intake was 101.5% of the recommendation, with 29.4% consuming <90 and 41.2% consuming >110% of the recommended amount. Protein intake was inadequate, with 82.4% consuming <90% of the recommended intake. Fiber intake was low in all the participants. Food texture aversion was common, with 66.7% of children aged >24 months requiring blended or pureed foods. A high proportion (85.3%) of families had a full-time at-home caregiver. As regards motor function, 82.4% of children aged >3 years were able to stand independently. Disease duration, but not protein intake, was a significant predictor of gross motor delay (adjusted r^2=0.89, P<0.001). In summary, the present study demonstrates that children with IOPD face significant nutritional and motor challenges despite ERT, leading to lower quality of life and a greater caregiving burden. Nutritional assessment, early and individualized interventions and psychosocial support are essential for improving long-term outcomes.

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Abbreviations: ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; IQR, interquartile range; GAA, acid alpha glucosidase; PD, Pompe disease

Key words: dietary intakes, infantile-onset Pompe disease, gross motor delay, malnutrition, nutrition practices, school attendance

Introduction

Pompe disease (PD), also known as type II glycogen storage disease, is a neuromuscular disease resulting from acid alpha glucosidase (*GAA*) gene mutations located on chromosome 17q25. This gene encodes the enzyme GAA, which is responsible for the breakdown of glycogen in lysosomes (1). The most commonly used classification of PD is based on the age of onset and the disease severity, which are associated with the residual activity of the enzyme. Minimal to absent GAA activity results in the early manifestation of the disease within the first few months of life; this early manifestation of the disease has been termed infantile-onset PD (IOPD). Children often present with hypotonia, muscle weakness, hypertrophic cardiomyopathy and eventually, cardiorespiratory failure if left untreated. In late-onset PD, the cardiac muscle is usually spared, while skeletal muscle function progressively deteriorates from limb-girdle weakness to respiratory insufficiency (2).

Although enzyme replacement therapy (ERT) has markedly improved the survival rate of patients, its impact on long-term functional outcomes and quality of life remains limited. Studies have demonstrated that despite the early initiation of ERT, a number of children continue to experience marked gross motor delays, feeding difficulties and dependency on caregivers for daily activities (2-6). These persistent challenges highlight the gap between clinical stabilization and real-world functional recovery. The present study therefore aimed to assess the developmental delay, nutritional intake and the caregiving burden among children with PD receiving long-term ERT, in order to better understand the residual impact of IOPD on daily life and identify areas where supportive care remains essential.

Patients and methods

Study design. The present single-center cross-sectional study was conducted at the Endocrinology, Genetics, Metabolism and Molecular Therapy Center of the Vietnam National Children's Hospital, Hanoi, Vietnam from November, 2021 to August, 2022.

Study subjects. Children diagnosed with PD at the Vietnam National Children's Hospital were enrolled based on the diagnostic criteria outlined in the 2006 guideline by the American

College of Medical Genetics and Genomics (ACMG) Work Group on Management of Pompe Disease (2).

Measurement of outcomes. Anthropometric measurements including weight and length/height were obtained using standardized methods and classified using the World Health Organization (WHO) growth standards (7,8). Nutrient intake was assessed via 24-h dietary recalls collected through caregiver interviews by a single nutritionist doctor.

School attendance and caregiving difficulties were evaluated using a structured caregiver questionnaire. Gross motor age was defined as the age corresponding to the furthest milestone based on the Denver Development Screening Test (9) successfully achieved by the child, at which 50% of age-matched peers are expected to have attained that skill. Gross motor delay was calculated by the difference between the gross motor age and the chronological age.

Statistical analysis. Data were analyzed using Stata 15.0 software (StataCorp LLC). Descriptive statistics were used to summarize demographic and outcome variables. Associations between variables were evaluated using linear regression for continuous outcomes, of which the dependent variable was the delay of the gross motor function based on the Denver Development Screening Test. The independent variables were the duration of the disease, the protein intake, the sex and the body mass index-for-age z-score. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

During the study period, 34 children with PD aged from 1-82 months (mean age, 32.8±23.1 months; of which 55.9% were male) were recruited. All patients had IOPD, and 33/34 patients (97.1%) had cardiac involvements (Table I). All patients received regular biweekly ERT, except during the Lunar New Year holiday and COVID-19 lockdown periods, when infusions were administered monthly. The cost of the enzyme was covered by pharmaceutical companies, while hospital bed charges and medical consumables were reimbursed by the national health insurance. The families of the patient were responsible for travel-related expenses, including transportation and meals.

Dietary intake analysis revealed that the median energy intake among the participants was 101.5% of the recommended value [interquartile range (IQR), 85.9-120.7%]. Of note, 29.4% (10/34) of children consumed <90% of their requirements, while 41.2% (14/34) exceeded 110% (Table II).

Protein intake was insufficient in the majority of patients, with a median intake of 3.5 g/kg/day (IQR, 1.8-4.7 g/kg/day). A total of 82.4% (28/34) of children consumed <90% of their estimated needs, while 17.6% (6/34) consumed >120% Table II). Fiber intake was low across all participants, with a mean intake of 2.1±1.8 g/1,000 kcal. None of the children met the threshold of 14 g/1,000 kcal, as recommended for an adequate fiber intake (Table II).

As regards food acceptance, 38.2% of the children exhibited 'picky' eating behaviors related to texture or food pieces. Among those aged >24 months, 66.7% still required food to be blended or pureed. As regards supplementation, 55.9% (19/34) were supplemented with vitamin D, with 78.9% of them receiving >400 IU per day. Among the children aged >3 years, 60% (9/15) used formula, of which 55.6% (5/9) were consuming growing-up formula, while the remainder were consuming standard follow-up formula.

In terms of daily functioning, the majority of children remained at home. Among the infants and toddlers, 15 of 17 were home-based, while 2 children remained hospitalized. Out of the preschoolers, 87.5% stayed at home, and only 1 child attended kindergarten. Similarly, 77.8% of the school-aged children were not attending school (Fig. 1).

The reasons for home care among the preschoolers and school-aged children (82.4% collectively) included prolonged mealtimes and special feeding (blended foods) requirements (58.8%), non-ambulatory status (17.6%), and, in one case, challenges involving 2 affected children in one household. The majority of families (85.3%) had a full-time at-home caregiver, typically a parent (93.1%). Gross motor ages were delayed by 22.5±20.5 months. Amongst the preschoolers and school-age children (>3 years of age), 82.4% were able to stand alone.

Table I. Characteristics of the study participants.

Demographic characteristics	
Age (months), mean ± SD	32.76±23.1
Infant and young children (≤3 years), n (%)	19 (55.9%)
Preschool (>3 to <6 years), n (%)	13 (38.2%)
School-aged (from 6 years), n (%)	2 (5.9%)
Sex, n (%)	
Male	19 (55.9%)
Female	15 (44.1%)
School attendance rate, n (%)	
Preschool (>3 to <6 years)	2 (15.4%)
School-aged (from 6 years)	1 (50%)
Clinical characteristics	
Clinical subtypes, n (%)	
Classical IOPD	33 (97.1%)
Modified IOPD	1 (2.9%)
CK (IU/l), mean ± SD	1451.56±897.02
AST (IU/l), mean ± SD	356.25±192.8
ALT (IU/l) (mean ± SD)	183.76±78.57
GAA activity essay using acarbose (mean ± SD)	93.4±2.4
CRIM status, n (%)[a]	
Positive	34 (100%)
Negative	0
Disease duration (months), mean ± SD	27.4±20.5

[a]CRIM status was determined by genotype-based prediction. IOPD, infantile-onset Pompe disease; SD, standard deviation; CK, creatine kinase; AST, aspartate transferase; ALT, alanine transaminase.

Table II. Adequacy of nutrient intake amongst children with IOPD.

Nutrient	Measure of central tendency	% Below recommendation	% Above recommendation	P-value
Energy adequacy[a]	Median 101.5% (IQR, 85.9-120.7)	29.4% (<90% of EER)	41.2% (>110% of EER)	0.0082
Protein intake[b]	Median 3.5 g/kg/day (IQR, 1.8-4.7)	82.4% (<90% of RNI)	17.6% (>120% of RNI)	<0.001
Fiber intake[c]	Mean 2.1±1.8 g/1,000 kcal	100% (<14 g/1,000 kcal)	0%	<0.001

[a]EER, estimated energy requirement based on age, sex and activity level; [b]RNI, recommended nutrient intake for protein based on WHO/FAO guidelines; [c]a cut-off of 14 g/1,000 kcal was used to indicate adequate fiber intake in children (extrapolated from adult values). Data were analyzed using a one-sample z-test for a proportion.

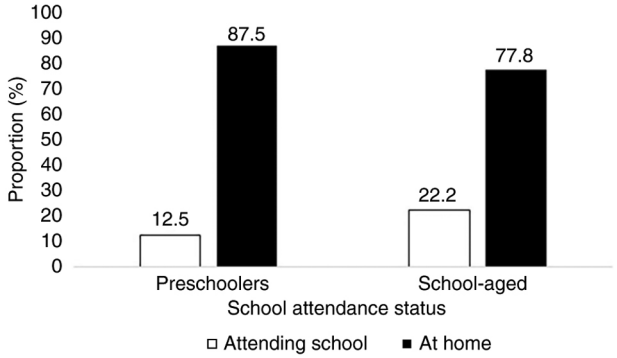

Figure 1. School attendance status of children with infantile-onset Pompe disease.

In the bivariate analysis, disease duration was found to be significantly associated with gross motor delay (adjusted r^2=0.89, P<0.001), while there was no statistically significant association between the protein intake and the gross motor delay (r^2=-0.0244, P=0.6472) (Table III).

Table III. Association of factors with gross motor delay.

Associating factors	β-coefficient	r^2 value	P-value
Protein intake (g/kg/day)	0.78	-0.0244	0.6472
Disease duration (months)	0.83	0.8788	<0.001

Discussion

The present study cohort exclusively comprised children with IOPD, which is the most severe phenotype, with almost all children presenting with cardiac involvement.

Dietary intakes and nutrition practices in children with IOPD. Energy-wise, intake varied widely, with almost a third of the children under-consuming and >40% exceeding recommendations. This variability may reflect the challenges in tailoring nutrition plans to individual clinical conditions, such as varying degrees of disease progression, immobility, feeding difficulties and metabolic demands. This was in accordance with the recommendations of regular nutritional assessment along the disease progression and individualized nutritional interventions (10-12).

Notably, >80% of children with IOPD in this cohort consumed <90% of their estimated protein needs. On the other hand, all participants failed to meet the fiber intake threshold of 14 g/1,000 kcal. These findings may be explained by the predominance of low-density liquid foods, such as formulas, purees and restricted diets. In fact, a notable proportion of children exhibited food refusal or required texture modification beyond toddler age. Systematic supplementation and the prolonged use of formula (to the extent of the high-energy growing formula) were current strategies to prevent micronutrient deficiencies. However, more global approaches including macronutrient considerations (e.g. protein and energy requirements), food texture sensitization in addition to oral motor function rehabilitation and orthodontic treatments may prove to be beneficial (13) and should be considered.

Gross motor delay, limited participation in school and care burden. In the present study cohort, 82.4% of the preschoolers and school-aged children (aged >3 years) were able to walk independently. This proportion is higher than that observed in some previous studies (25-64%) (14-16), which may be due to the fact that the participants in the present study were younger (mean age, 32.8±23.1 months) and had a shorter disease duration. Furthermore, 100% of the patients in the present study were CRIM-positive, which is typically associated with a better response to ERT. In a German-Austrian cohort, in which 86.7% of the patients were CRIM-positive, the independent ambulation status declined in the 7-year follow-up from 46.7% (median age of 2 years) to 33.3% (median age of 9.1 years) (16). In another study, in a UK multicenter population, the mean ERT duration was 13 years 9 months and the CRIM-positive rate was 55%; in that study, 30% of patients achieved independent ambulation (17).

Of note, a significant proportion (17.2%) of the present study subgroup (>3 years of age) with a median ERT duration of 40.5 months remained non-ambulant, suggesting that ERT alone may not be sufficient to prevent long-term motor deterioration. This highlights the need for early intervention and additional therapeutic strategies beyond ERT in order to improve motor outcomes and preserve function over time.

The present study also demonstrated that the care burden on families was considerable, with 85.3% of households having a full-time at-home caregiver, most often a parent. This reflects the substantial demands of daily care, including prolonged mealtimes, specialized feeding practices and physical

assistance due to limited mobility. Similar findings have been reported in previous studies, where caregivers of children with IOPD experience high levels of emotional, physical and financial stress (18,19). The requirement for continuous care may limit parental employment and social participation, underscoring the need for structured psychosocial support and access to community-based services.

The present study has certain limitations, which should be mentioned. The present study was limited by the cross-sectional design, small sample size and reliance on caregiver-reported intake, which may be subject to recall bias. Moreover, the cross-sectional design cannot infer causal associations; therefore, further studies with larger sample sizes and a longitudinal design are warranted. Nonetheless, the present study provides valuable insight into the real-world challenges of managing nutrition and development in children with IOPD.

In conclusion, children with IOPD face significant nutritional and motor challenges despite ERT. Suboptimal protein and fiber intake, along with high variabilities in energy needs, highlight the importance of tailored nutritional care. Although the ambulation rates in the present study cohort were higher than those in other studies, motor delays remain common, reinforcing the need for early and multidisciplinary interventions. The high caregiving burden further emphasizes the need for broader family support.

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Availability of data and materials

The data generated in the present study are not publicly available due to ethical restrictions, but may be requested from the corresponding author.

Authors' contributions

TMTL conceptualized and designed the study, collected and analyzed the data, performed a literature search, interpreted the results and drafted the manuscript. ATP was responsible for dietary recalls, anthropometric measurements, nutritional interventions and was also involved in drafting the manuscript. CDV was responsible for clinical examinations, interpreted the results and performed a literature search. PNT interpreted the imaging results (interpretation of chest X-rays to assess cardiomegaly), and performed the literature search. TTHN contributed to the nutritional interventions, patient management, was involved in drafting the manuscript. NKN conducted the clinical examinations, and critically revised the manuscript for important intellectual content. TMTL and ATP confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Vietnam National Children's Hospital, Hanoi, Vietnam (2176-BVNTW-HĐĐĐ). Written informed consent was obtained from the caregivers of all participants prior to enrollment. Participation was entirely voluntary, and caregivers were informed that they could withdraw from the study at any time without any impact on the patient's care. All collected data were anonymized and used exclusively for research purposes.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the authors did use artificial intelligence assisted tools in order to improve the readability and language of the manuscript. After using this tool service, the authors did review and edit the content as needed, taking full responsibility for the content of the publication.

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