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Evaluation of Pompe Disease from a Broad and Systemic Perspective

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ABSTRACT

Pompe disease is a lysosomal storage disorder caused by α-1,4-glucosidase deficiency. The broad spectrum of clinical manifestations results from glycogen accumulation in the muscles and central nervous system (CNS). In this study, we aimed to evaluate the clinical course of Pompe disease. This brief report included six patients. The collected data included demographic characteristics, clinical findings, echocardiography, electroencephalography, electromyography, and brain magnetic resonance imaging. High-dose enzyme replacement therapy reduced the severity of hypertrophic cardiomyopathy in patients with infantile-onset Pompe disease. Three patients exhibited speech difficulties, one patient was diagnosed with epilepsy, and MRI revealed white matter abnormalities in three patients. The neurological findings observed in patients with CNS involvement suggest that those with infantile-onset Pompe disease should be closely monitored for neurocognitive development. Novel treatments capable of crossing the blood-brain barrier may benefit these patients.

Keywords: α-1,4-glucosidase deficiency, cardiomyopathy, Pompe disease.

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INTRODUCTION

Pompe disease (α-1,4-glucosidase deficiency, OMIM #232300) is a lysosomal storage disorder caused by autosomal recessive mutations in the GAA gene. These mutations result in loss of α-1,4-glucosidase function, leading to excessive glycogen accumulation in tissues, particularly the myocardium and skeletal muscles. Pompe disease is classified into two subgroups based on age at onset, organ involvement, and the rate of disease progression: infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD).[1,2]

Infantile-onset Pompe disease typically manifests with hypertrophic cardiomyopathy, generalized muscle weakness, and hypotonia within the first few months of life. In most untreated cases, death occurs within the first year of life due to cardiorespiratory failure.[2]

Alglucosidase alfa, an enzyme replacement therapy (ERT) approved by the US Food and Drug Administration (FDA) in 2006, is used to treat Pompe disease.[3] Before ERT was introduced into clinical practice, patients with IOPD and hypertrophic cardiomyopathy typically died before reaching 1 year of age because effective treatment was unavailable.[4] However, an increased frequency of central nervous system (CNS) findings associated with prolonged survival has been reported in patients with IOPD because ERT is unable to cross the blood-brain barrier.[5]

In this study, we aimed to evaluate the echocardiographic, clinical, and CNS findings of six patients with Pompe disease who received ERT at our clinic.

METHODS

This retrospective, single-center cohort study included six patients who were diagnosed with Pompe disease and followed up in the Nutrition and Metabolism Department of Erciyes University between June 2008 and May 2023.

All procedures conducted in studies involving human participants adhered to the ethical standards of the institutional and/or national research committee, the 1964 Declaration of Helsinki and its subsequent amendments, or comparable ethical standards. The study was approved by Erciyes University Clinical Research Ethics Committee (Approval Number: 2023/610, Date: 25.09.2023).

Data on demographic characteristics, clinical findings, muscle enzyme measurements, genetic analyses, and the results of echocardiography (ECHO), electroencephalography (EEG), electromyography (EMG), and brain magnetic resonance imaging (MRI) were recorded.

Statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria; available online at http://www.r-project.org/).

RESULTS

Among the patients, one was diagnosed with LOPD and five with IOPD. The median age of the participants was 90 (62.3–130.5) months, and 33.3% (n=2) were female. The parents of 50% (n=3) of the patients were consanguineous. The median age at diagnosis was 3.5 (1–25.5) months, the median birth weight was 3400 (2800–3795) g, and the median gestational age at birth was 39.5 (38–40) weeks. For patients with IOPD, treatment was initiated at a median age of 3 (1–6) months, whereas treatment for the patient with LOPD was initiated at 84 months. The patients received ERT for a median duration of 87.5 (57–108.8) months. Table 1 provides details on the patients' ages, treatment durations, and enzyme and molecular analysis results.

Patients with IOPD presented with hypotonia, respiratory distress, and cyanosis, whereas the patient with LOPD presented with gait disturbance and fatigue. Speech difficulties were observed in 50% (n=3) of the patients, and one patient had difficulty rising from a seated position. Details of the physical examination findings are presented in Table 1.

Patients #2 and #3 experienced seizures, and EEG revealed epilepsy in patient #2, prompting the initiation of antiepileptic treatment. Table 1 summarizes the EEG, EMG, and brain MRI findings.

Patient #1, who was subsequently diagnosed with LOPD, was referred to our clinic after an elevated CK level was detected. Alpha-glucosidase activity was measured at 1.13 µmol/L (reference range: 1.5–10) by leukocyte enzyme analysis, and a single variant allele, c.32-13T>G (2737del), was identified in the GAA gene. Alpha-glucosidase activity was remeasured to confirm the diagnosis (0.9 µmol/L). Genetic analysis of the parents identified a single c.32-13T>G (2737del) variant allele in the GAA gene in the mother. Alpha-glucosidase activity was normal in both parents. Myogenic motor unit potentials (MUPs) were detected on the patient's EMG. Because the clinical and laboratory findings were consistent with LOPD and no alternative causes could explain the symptoms or laboratory findings, the patient was diagnosed with LOPD. ERT was initiated at a dose of 40 mg/kg every 2 weeks.

At diagnosis, the patient's pulmonary function tests showed a forced expiratory volume in 1 second (FEV1) of 111.7% and a forced vital capacity (FVC) of 94.8%. After treatment, pulmonary function tests showed an FEV1 of 124% and an FVC of 125.2%. On the 6-minute walk test, the patient walked 440 m at diagnosis, and this distance remained unchanged at the end of the second year of treatment.

DISCUSSION

This study showed that the CNS manifestations of IOPD become more apparent over time. As ERT prolongs survival in patients with IOPD, the management of IOPD may require more extensive CNS evaluation. This finding also suggests a need for novel therapies to address the progression of neurological symptoms.

A comprehensive investigation by the Infantile-Onset Pompe Disease Natural History Study Group found that the mean age at symptom onset in patients with IOPD was 2 months and that the mean age at diagnosis was 4.7 months.[6] Similarly, our study showed that the mean age at diagnosis of Pompe disease was 3.5 months.

Khan et al.[7] reported that high-dose ERT reduced the need for mechanical ventilation in patients with Pompe disease

Table 1. Clinical, laboratory, and imaging findings of the patients

Patient	P1	P2	P3	P4	P5	P6
Age (months)	204	68	106	90	45	90
Age at diagnosis (months)	84	6	1	1	3	4
ERT duration (months)	120	62	105	89	42	86
Enzyme activity (μmol/L/s) (reference range: 1.5–10)	1.13	0.2	N/A	0.17	0.76	0.73
GAA gene	c.32-13T>G, heterozygous	c.896T>G, heterozygous; c.2662G>A, heterozygous	c.2646+2T>A, homozygous	c.266G>A, homozygous; c.2303C>G, homozygous	c.2456G>C, homozygous	c.2104C>T, homozygous
AST (0–32 U/L)	145	273	86	122	189	159
CPK (26–192 U/L)	1409	867	534	450	600	596
Presenting symptom	Gait disturbance, fatigue	Hypotonia	Respiratory distress	Hypotonia	Respiratory distress	Cyanosis after birth
Speech difficulties	–	+	+	–	–	+
Mechanical ventilation requirement	–	–	–	–	–	–
Difficulty standing up	–	–	–	–	–	+
Independent walking	–	–	–	–	–	–
Need for wheelchair	–	–	–	–	–	–
Supraventricular tachycardia	–	+	–	–	+	+
Seizure	–	+	+	–	–	–
EEG	N/A	High-amplitude delta-frequency, sharply contoured wave activity in the posterior hemisphere	Normal	N/A	N/A	N/A
EMG	Myogenic MUPs	N/A	N/A	Myogenic MUPs	N/A	N/A
Age at brain MRI (years)	13	2	7	4	N/A	4

Table 1 (cont). Clinical, laboratory, and imaging findings of the patients

Patient	P1	P2	P3	P4	P5	P6
Brain MRI	Normal	Normal	Widespread patchy and confluent T2/FLAIR signal increases in the bilateral cerebral hemispheric white matter, extending from the subcortical regions to the periventricular areas and internal capsules. The corpus callosum is thinned.	Symmetrical T2/FLAIR hyperintense signal abnormalities in the bilateral centrum semiovale and periventricular deep white matter. Symmetrical lesions are present in the bilateral deep cerebral white matter.	N/A	Symmetrical T2/FLAIR signal increases at the bilateral supraventricular level. The corpus callosum is present in the midline and appears diffusely thinned.
ECHO (at diagnosis)	Normal	Hypertrophic cardiomyopathy	Hypertrophic cardiomyopathy	Normal	Hypertrophic cardiomyopathy	Hypertrophic cardiomyopathy
ECHO (last examination)	Normal	Mild left ventricular hypertrophy	Mild left ventricular hypertrophy	Normal	Hypertrophic cardiomyopathy	Mild hypertrophic cardiomyopathy

ERT: Enzyme replacement therapy; EEG: Electroencephalography; EMG: Electromyography; MRI: magnetic resonance imaging; ECHO: Echocardiography.

by improving respiratory function.[7] No patients in our study required a wheelchair or respiratory support. After ERT, the patient with LOPD demonstrated increases in FEV1 and FVC, indicating improved pulmonary function. This finding was consistent with previous studies reporting a positive association between ERT duration and respiratory function and muscle strength in patients with LOPD.[7,8]

Speech and swallowing difficulties are observed in patients with Pompe disease because of impaired respiratory and orofacial muscle function. In addition, impaired myelination and neuronal cell loss in Pompe disease may exacerbate neurological symptoms. In a study by Su et al.,[9] which evaluated 14 patients with Pompe disease, speech impairments were detected in two-thirds of the patients. In our study, speech difficulties were observed in half of the patients.

Compared with LOPD, IOPD is more severe, and ERT has been shown to improve survival in patients with IOPD. Previous research indicates that some cognitive abilities and neurological functions may deteriorate as survival is prolonged in patients with IOPD.[5] Indeed, postmortem examinations of patients with IOPD have revealed glycogen deposits in brain tissue, particularly in glial cells of the brainstem, thalamus, basal ganglia, hippocampus, and cerebellum.[10] Because current ERT cannot cross the blood-brain barrier, it is ineffective in preventing glycogen accumulation in the brain. In this study, MRI scans revealed periventricular deep white matter abnormalities, indicating progressive brain damage, in three patients with IOPD. This finding suggests that the management of IOPD may require more extensive CNS evaluation as patients age and that novel ERT capable of crossing the blood-brain barrier is needed. In contrast, Van den Dorpel et al.[11] reported no abnormalities on brain MRI in patients with LOPD. Similarly, the patient with LOPD in our study had a normal brain MRI scan. This finding may result from greater residual enzyme activity in patients with LOPD, which may protect against brain damage.[11]

EEG was performed in two patients after the onset of seizures. Of these two patients, one was diagnosed with epilepsy. Kenney-Jung et al.[12] reported six patients with IOPD and CNS symptoms, noting that epilepsy was identified in five of them. The authors also reported no comorbidities in patients with epilepsy. Similarly, the patient with IOPD and epilepsy in our study had no comorbidities or family history of epilepsy. The lower rate of epilepsy in our study compared with that reported by Kenney-Jung et al.[12] (20% vs. 83.3%) may be attributable to the shorter follow-up period in our study. Our finding, which is consistent with the literature, highlights the importance of awareness of the potential development of epilepsy in patients with IOPD.

This study has several limitations. Owing to the rarity of Pompe disease, only six patients could be enrolled despite a 15-year recruitment period. Longer follow-up periods are needed to more clearly delineate the progression of CNS involvement.

Our study demonstrated that CNS involvement worsened over time. With the improvement in life expectancy achieved by ERT, the management of CNS manifestations is likely to become increasingly important in the long-term care of patients with IOPD. This finding also highlights the unmet need for next-generation ERT formulations capable of crossing the blood-brain barrier to prevent progressive neurological damage. These findings further emphasize the need for enhanced supportive care strategies in the long-term management of IOPD.

Ethics Committee Approval: Ethics committee approval was obtained from Erciyes University Clinical Research Ethics Committee (Approval Number: 2023/610, Date: 25.09.2023).

Informed Consent: Written informed consent was not required due to the retrospective nature of this study.

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