Very Early Treatment for Infantile-Onset Pompe Disease Contributes to Better Outcomes

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Objective To evaluate whether very early treatment in our patients would result in better clinical outcomes and to compare these data with other infantile-onset Pompe disease (IOPD) cohort studies.

Methods In this nationwide program, 669 797 newborns were screened for Pompe disease. We diagnosed IOPD in 14 of these newborns, and all were treated and followed in our hospital.

Results After 2010, the mean age at first enzyme-replacement therapy (ERT) was 11.92 days. Our patients had better biological, physical, and developmental outcomes and lower anti-rh acid α-glucosidase antibodies after 2 years of treatment, even compared with one group that began ERT just 10 days later than our cohort. No patient had a hearing disorder or abnormal vision. The mean age for independent walking was 11.6 $\pm$ 1.3 months, the same age as normal children.

Conclusions ERT for patients with IOPD should be initiated as early as possible before irreversible damage occurs. Our results indicate that early identification of patients with IOPD allows for the very early initiation of ERT. Starting ERT even a few days earlier may lead to better patient outcomes. *(J Pediatr 2016;169:174-80)*.

Pompe disease is an autosomal-recessive lysosomal storage disorder characterized by the deficiency of acid α-glucosidase (GAA),[1,2] which leads to the progressive accumulation of glycogen in numerous types of cells and tissues.[3,4] A broad spectrum of clinical phenotypes is observed, ranging from the severe, rapidly progressive infantile-onset Pompe disease (IOPD) characterized by cardiac involvement to the attenuated, late-onset Pompe disease.[5-7] Early enzyme-replacement therapy (ERT) with recombinant human alglucosidase alpha (Myozyme; Genzyme, Boston, Massachusetts) can prolong survival and improve the long-term outcome of patients with IOPD.[6,8,9] Nevertheless, it remains unknown whether therapeutic outcomes differ between very early (10 days of age) and early (1 month of age) IOPD treatment.

Newborn screening is the only way to initiate the early diagnosis and treatment of Pompe disease.[8,9] However, even when the newborn screening is used, the earliest mean age at the start of ERT is about 21 days.[10] The Taipei Veterans General Hospital (TVGH) began Pompe newborn screening in 2008, testing approximately two-thirds of the newborn population in Taiwan.[4,6,8] By 2010, we had established an effective newborn screening program with rapid diagnostic strategies,[4] and almost all of the infants with suspected IOPD could be diagnosed correctly within 2 hours and receive ERT within 4 hours of admission. With such an effective system, most of our patients with IOPD started their ERT at about 11 days of age. In this 6-year cohort study, we report the prognosis of 14 patients with IOPD who received very early ERT and compare these results with those of similar cohorts. Furthermore, we compare the outcomes of 5 patients with IOPD who have identical GAA gene mutations to disclose possible differences between few days earlier treatment.

Methods

Pompe disease screening was added to the newborn screening system in Taiwan in 2008. In this nationwide program, 669 797 newborns were screened for Pompe

AST	Aspartate aminotransferase
Bayley-III	Bayley Scale of Infant and Toddler Development, Third Edition
CK	Creatine kinase
CRIM	Cross-reactive immunologic
ERT	Enzyme-replacement therapy
GAA	Acid α-glucosidase
IOPD	Infantile-onset Pompe disease
LDH	Lactate dehydrogenase
LVMI	Left ventricular mass index
PDMS-II	Peabody Development Motor Scale, Second Edition
TVGH	Taipei Veterans General Hospital

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disease between January 1, 2008, and January 31, 2014. Dried blood spot screening was conducted at the Taipei Institute of Pathology and Chinese Foundation of Health newborn screening centers with the use of a fluorescence (4-methylumbelliferone) assay; this test was changed to the tandem mass spectrometry method after 2010. Infants with GAA activity ≤0.50 mmol/L/h (normal activity >2.0 mmol/L/h) were referred immediately to the TVGH for diagnostic confirmation. The study population included all infants with IOPD who were referred to the TVGH between January 2008 and January 2014. The study protocol was approved by the Institutional Review Board of the TVGH.

Physical examinations, blood tests, and echocardiography were performed within 2 hours upon referral of infants. Blood samples were assessed for creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and lymphocyte GAA enzymatic activity. After 2010, all transferred newborns were started on ERT within 4 hours of admission if they had the following manifestations: (1) general weakness; (2) extremely low initial GAA activity (<0.50 mmol/L/h); (3) elevated CK (>250 U/L); and (4) elevated left ventricular mass index (LVMI; >80 g/m^2). Quadriceps muscle biopsies and GAA gene sequencing were performed after parental informed consent was obtained.

All confirmed patients with IOPD underwent regular ERT and physical therapy every 2 weeks thereafter. Echocardiography was performed monthly for 6 months and then once every 3-6 months. Blood tests for CK, LDH, and AST were performed monthly for 6 months and then once every 3 months. The level of anti-rh GAA antibodies titer to ERT was determined before ERT and 1 and 2 years after ERT. Developmental surveys were conducted with the Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III), and the Peabody Development Motor Scale, Second Edition (PDMS-II).[11]

Statistical Analyses

Data are presented as the median with range and mean ± IQR. Statistical tests were performed by the

Table I. Patient characteristics of 14 patients with IOPD

Patient no.	Sex	GA, wk, BBW, kg	Age at referral, d	Age at first ERT, d	End-of-study age, mo	End-of-study BH, cm (percentile)	End-of-study BW, kg (percentile)	GAA mutation
1	F	38, 3.1	51	79	64	110 (15-50)	18.3 (15-50)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
2	F	37, 3.2	18	18	61	108 (15-50)	18 (3-15)	c.1411_1414del, (E471fsX5), heterozygous c.872 T→C, (p.L291P) heterozygous
3	M	38, 3.5	15	15	49	100.5 (15)	15.8 (15-50)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
4	M	39, 3.3	9	9	48	100 (15-50)	17.5 (50-85)	c.1935 C→A, (p.D645E), heterozygous c.2303 C→T, (p.P768L), heterozygous
5	M	38, 3.1	12	12	39	97 (15-50)	17 (50-85)	c.1396 G→T, (p.V466F), heterozygous c.1935 C→A, (pD645E), heterozygous
6	F	39, 3.0	9	9	37	95 (15-50)	15 (50-85)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
7	F	39, 3.1	8	23	26	88 (50)	12.6 (50)	c.2238 G→C, (p.W746C), heterozygous c.2237 G→A, (p.W746X), heterozygous c.1726 G→A, (p.G576S), heterozygous
8	F	34, 2.2	12	12	25	85 (15-50)	12 (50)	c.1935 C→A, (pD645E), heterozygous IVS7+2 T→C, heterozygous c.1726 G→A, (p.G576S), heterozygous
9	M	39, 3.7	7	7	24	86 (15-50)	11.9 (15-50)	IVS7+2 T→C, heterozygous c.1935 C→A, (p.D645E), heterozygous c.1726 G→A, (p.G576S), heterozygous
10	M	39, 2.9	13	13	24	85 (15-50)	12.0 (15-50)	c.1082 C→T, (p.P361L), heterozygous c.1935 C→A, (p.D645E), heterozygous c.1726 G→A, (p.G576S), heterozygous
11	F	39, 2.9	10	10	20	91 (97)	11 (50)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
12	F	41, 2.6	6	6	15	78 (15-50)	8.5 (3-15)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
13	F	36 ± 5, 3.3	8	8	14	80 (85)	12.15 (97)	c.1411_1414del, (E471fsX5), heterozygous c.1935 C→A, (pD645E), heterozygous c.1726 G→A, (p.G576S), heterozygous
14	M	39 ± 5, 2.49	13	13	13	75 (3-15)	9 (15)	c.1726 G→A, (p.G576S), heterozygous c.1935C→A, (pD645E), heterozygous c.2274insC, (p.G759fs), heterozygous
Mean		38.3 ± 1.5, 3.02 ± 0.38	3.02 ± 0.38	11.92 ± 4.53*	32.7 ± 16.4	38.8 ± 23.1th (percentile)	43.5 ± 24.4th (percentile)	-

BBW, birth BW; *BH*, body height; *BW*, body weight; *F*, female; *GA*, gestational age; *M*, male.
*Excludes patient 1 (diagnosed before 2010).