Reversal of Cardiac Dysfunction after Enzyme Replacement in Patients with Infantile-Onset Pompe Disease

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Objective To compare the effects of enzyme replacement therapy (ERT) on cardiac performance in symptomatic and symptom-free infants with Pompe disease.

Study design Patients diagnosed between 1983 and 2008 were identified. Before the initiation of ERT, systolic dysfunction appeared only in patients ≥5 months; thus we used this cut-point in age to divide clinically symptomatic patients into early and late treatment groups (Clin-E and Clin-L). Newborn screening (NBS) identified symptom-free patients.

Results Among a total of 40 patients, 14 received ERT: 5 in the Clin-L, 4 in the Clin-E, and 5 in the NBS groups. All patients showed cardiomegaly, hypertrophic myocardium, and elevated B-type natriuretic peptide (measured in the Clin-E and NBS groups). ERT improved the survival and outcomes. Regressed myocardial hypertrophy and lowered B-type natriuretic peptide level occurred after 1 to 6 months of ERT. Nonetheless, there were 2 deaths and 2 survivors requiring ventilator support in the Clin-L group. Despite the regressed QRS voltage and shortened QT dispersion, life-threatening arrhythmias were still observed in 3, but none in the NBS group.

Conclusion ERT may restore the cardiac function in both symptomatic and symptom-free patients, but the beneficial effect may be unpredictable if given after the age of 5 months. *(J Pediatr 2009;155:271-5)*.

Pompe disease is an autosomal recessive disease caused by the deficiency of the glycolytic lysosomal enzyme acid α-glucosidase (GAA). This enzyme defect results in the accumulation of glycogen within the lysosomes, especially in smooth, skeletal, and cardiac muscle cells.[1] Patients with infantile-onset Pompe disease usually present with hypotonia, generalized muscle weakness, and hypertrophic cardiomyopathy in early infancy.[2] A short PR interval and a large QRS complex are the characteristic electrocardiographic changes.[3] Most patients die of cardiopulmonary failure before the age of 1 year.[4-6] Enzyme replacement therapy (ERT) with recombinant human GAA has been recently shown to effectively reduce left ventricular (LV) mass, improve cardiac function and remodel the conduction abnormalities.[7-9] Furthermore, the success of newborn screening (NBS) for Pompe disease made early administration of ERT possible in symptom-free patients.[10] However, the impact of the timing of ERT initiation on the reversal of cardiac dysfunction has never been examined. The purpose of this study was to explore the association between clinical status at ERT initiation and the effects of ERT on cardiac performance in patients with infantile-onset Pompe disease.

Methods

Patients diagnosed with infantile-onset Pompe disease from January 1983 to March 2008 were identified from the patient database of the National Taiwan University Hospital. The diagnosis was confirmed by endogenous GAA enzyme activity being less than 5% of the normal mean in mononuclear blood cells.[10] Twenty-six patients were born before June 2002 (the pre-ERT era), and all died before ERT was available. An additional 14 patients were born after or survived to December 2002 (the post-ERT era) when ERT with intravenous recombinant human GAA (20mg/kg, every other week) was started in all patients.

Data from the patients who did not receive ERT (n = 26) and the pre-ERT data from patients who later received ERT (n = 14) were used to investigate the natural course of ventricular dysfunction in infantile-onset Pompe disease. We found that systolic

BNP	B-type natriuretic peptide
ECG	Electrocardiogram
ERT	Enzyme replacement therapy
GAA	Acid-α glucosidase
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
NBS	Newborn screening
QTc	Corrected QT interval
QTd	QT dispersion

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Table I. Clinical characteristics of the 14 patients with infantile-onset Pompe disease receiving ERT

Patients	Age at diagnosis (mo)	Age at starting ERT (mo)	Initial symptoms	Initial signs	Arrhythmias after ERT	Morbidity or death	Duration of ERT (years)
Clin-L 1	3.03	6.07	Hypo/F/T	C/M/H/L	Preexcitation	Ve/Je/B	5.21
Clin-L 2	4.07	5.67	Hypo	C/M/H/L	—	Ve/Je/B/D	1.15
Clin-L 3	4.97	5.87	Hypo	C/M/L	Bradycardia	Ve/Je/B	4.45
Clin-L 4	2.77	5.53	F	C/M/H/L	—	Ve/Je/B/D	3.54
Clin-L 5	6.20	6.47	Hypo	C/M/H/L	SVT	—	4.23
Clin-E 1	4.02	4.37	Hypo/T	C/M/H/L	Pulseless VT	—	2.04
Clin-E 2	2.63	2.90	F	C/M/L	—	—	1.55
Clin-E 3	3.40	3.47	Hypo/F	C/M/L	VPC and non-sustained VT	—	0.36
Clin-E 4	1.60	1.63	Hypo/F	C/M/L	—	—	0.32
NBS 1	19 days	26 days	—	C/M	—	—	1.77
NBS 2	22 days	29 days	—	C/M/L	JPC	—	1.72
NBS 3	9 days	17 days	—	C/M	—	—	1.12
NBS 4	30 days	34 days	—	C/M	—	—	0.56
NBS 5	10 days	12 days	—	C/M	—	—	0.26

Hypo, Hypotonia; *F,* feeding problem; *T,* tachypnea; *C,* cardiomegaly; *M,* elevated muscle enzyme (creatinine kinase); *H,* hepatomegaly; *L,* elevated liver enzyme (alanine transaminase); *Ve,* ventilator dependence; *Je,* jejunostomy; *B,* bed ridden; *D,* dead; *SVT,* supraventricular tachycardia; *VPC,* ventricular premature contractions; *JPC,* junctional premature contractions.

dysfunction (defined as a left ventricular ejection fraction [LVEF] < 40% by echocardiography) appeared only after the age of 5 months in all 40 patients (Figure 1; available at www.jpeds.com). Therefore, for all clinically symptomatic patients included in the prospective study (described below), a cut-off age of 5 months at the start of ERT was used to divide clinically symptomatic patients into clinically symptomatic: early treatment (Clin-E) and clinically symptomatic: late treatment (Clin-L) groups.

The NBS program for Pompe disease, conducted by the newborn screening center of the National Taiwan University Hospital, was implemented in October 2005.[10] This program screened approximately 45% of all babies born in Taiwan and has successfully identified clinically symptom-free infants with Pompe disease.[11] Patients identified by the NBS program constituted the NBS group of this study. The study protocol was approved by the institutional review board of our institution and informed consent was obtained for each blood sample collected. Serial echocardiographic examinations were prospectively performed to determine LV mass and LVEF with 2-dimensional echocardiography in all patients after receiving ERT.[12] Standard 12-lead electrocardiography (ECGs) was performed at baseline and before each course of ERT. The shortest PR intervals among all 12 leads defined the PR interval of each ECG tracing. The QT interval was measured on lead II or V5 to avoid the interference

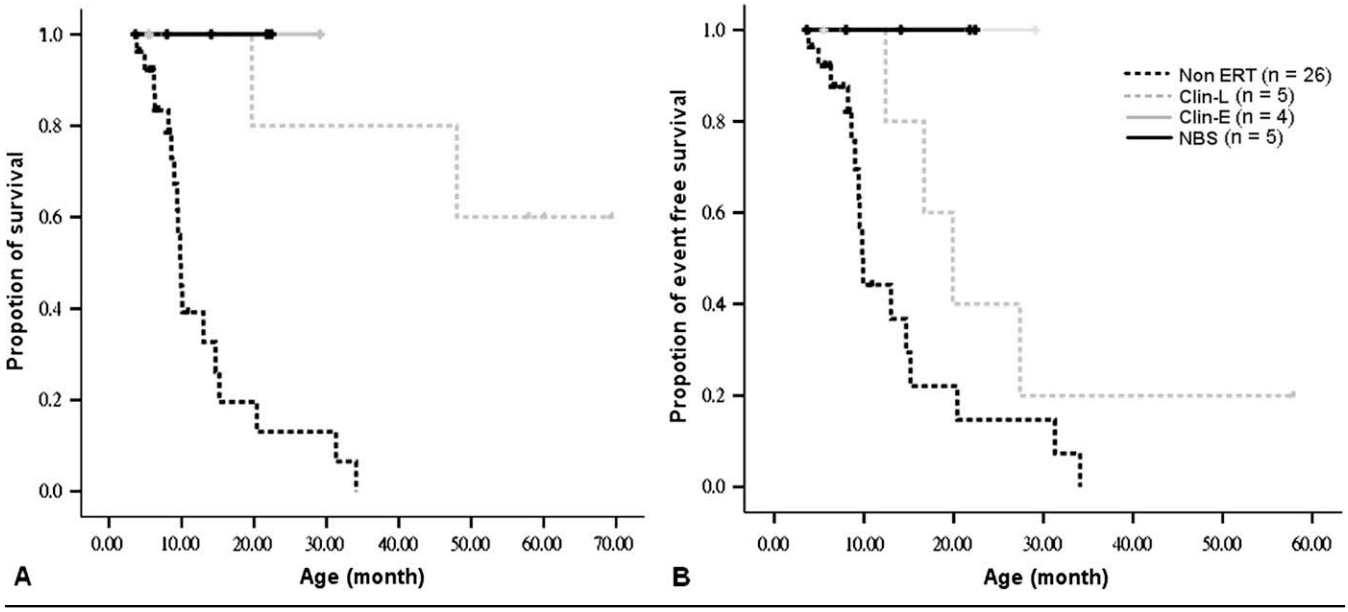

Figure 3. **A**, The survival curves and **B**, event- (death or long-term ventilator dependence) free survival curves in different groups of patients with infantile-onset Pompe disease.