Long-Term Prognosis of Patients with Infantile-Onset Pompe Disease Diagnosed by Newborn Screening and Treated since Birth

Yin-Hsiu Chien, MD, PhD[1,2], Ni-Chung Lee, MD, PhD[1,2], Chun-An Chen, MD[2], Fuu-Jen Tsai, MD, PhD[3], Wen-Hui Tsai, MD, PhD[4], Jeng-Yi Shieh, MD, PhD[5], Hsiang-Ju Huang, MS[6], Wei-Chung Hsu, MD, PhD[7], Tzu-Hsun Tsai, MD, PhD[8], and Wuh-Liang Hwu, MD, PhD[1,2]

Objective To determine the benefit of newborn screening for the long-term prognosis of patients with classic infantile-onset Pompe disease (IOPD).

Study design A cohort of patients with classic IOPD were diagnosed by newborn screening, treated with recombinant human acid α-glucosidase (rhGAA), and followed prospectively. Outcome measurements included survival, left ventricular mass, serum creatinine kinase, motor function, mental development, and systemic manifestations.

Results Ten patients who presented with left ventricular hypertrophy at diagnosis received rhGAA infusions starting at a median age of 16 days (6-34 days). All patients were cross-reactive immunologic material-positive. After a median treatment time of 63 months (range 28-90 months), all could walk independently, and none required mechanical ventilation. All patients had motor capability sufficient for participating in daily activities, but muscle weakness over the pelvic girdle appeared gradually after 2 years of age. Ptosis was present in one-half of the patients, and speech disorders were common. Anti-rhGAA antibody titers were low (median maximal titer value 1:1600, range: undetectable ~ 1:12 800).

Conclusion By studying patients treated since birth who have no significant anti-rhGAA antibody interference, this prospective study demonstrates that the efficacy of rhGAA therapy is high and consistent for the treatment of classic IOPD. This study also exposes limitations of rhGAA treatment. The etiology of the manifestations in these early-treated patients will require further study. *(J Pediatr 2015;166:985-91)*.

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Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is a lysosomal disorder in which a deficiency of acid α-glucosidase (GAA, EC 3.2.1.20) causes the intralysosomal accumulation of glycogen in all tissues, most notably in skeletal muscles.[1] Clinically, patients with Pompe disease present with a wide spectrum of symptoms, ranging from severe rapidly progressive classic infantile-onset Pompe disease (IOPD), which usually presents with hypertrophic cardiomyopathy, to slowly progressive later-onset forms with muscular weakness that can occur from early childhood to late adulthood and typically occur without cardiac manifestations. In patients with classic IOPD, symptoms start very early in life (median age of 2 months), and death occurs soon after if the patients remain untreated (median age of 8.7 months).[2,3]

Enzyme-replacement therapy (ERT) with recombinant human GAA (rhGAA)[4,5] is the only treatment available for patients with Pompe disease. In the pivotal trial of rhGAA, all patients survived to 18 months of age, and a Cox proportional hazards analysis demonstrated that rhGAA treatment reduced the risk of death or invasive ventilation by 92%.[6] The Kaplan-Meier invasive ventilation-free survival rate, however, decreased to 66.7% at age 24 months and 49.4% at age 36 months.[7] Patients with cross-reactive immunologic material (CRIM)-negative IOPD tend to develop a high titer of antibodies,[8] and CRIM-negative status predicts reduced survival and poorer clinical outcomes.[9] Nevertheless, 14 of the aforementioned 18 patients were CRIM-positive. In another

CK	Creatinine kinase
CRIM	Cross-reactive immunologic material
ERT	Enzyme-replacement therapy
GAA	Acid α-glucosidase
IOPD	Infantile-onset Pompe disease
LVMI	Left ventricular mass index
MRI	Magnetic resonance imaging
NBS	Newborn screening
PDMS-II	Peabody Developmental Motor Scale, Second Edition
Pompe-PEDI	Pediatric Evaluation of Disability Inventory specific for Pompe disease
rhGAA	Recombinant human acid α-glucosidase

From the [1]Department of Medical Genetics and [2]Department of Pediatrics, National Taiwan University Hospital, Taipei; [3]Department of Pediatrics and Medical Genetics, China Medical University Hospital, Taichung; [4]Department of Pediatrics, Chi-Mei Medical Center, Tainan; [5]Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital; [6]Department of Rehabilitation Medicine, Chen-Hsin Hospital; and Departments of [7]Otolaryngology and [8]Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan

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clinical trial with 21 patients treated for a median duration of 120 weeks, invasive ventilator free survival was 44%, and 19 of the 21 patients were CRIM-positive.[10] Outside of these clinical trials, the survival of IOPD patients is not clear.

Other clinical sequelae also have been observed in long-term survivors with IOPD. Survivors present with respiratory failure and an inability to walk[11] or have the ability to walk independently with residual myopathy, including generalized weakness/hypotonia, decreased endurance, persistent fatigue,[11] arrhythmia,[12] gastroesophageal reflux,[11] ptosis,[11,13] hearing loss,[11,14] hypernasal speech with a flaccid dysarthria and/or oropharyngeal dysphagia,[13,15] and abnormalities in brain myelination.[14,16] The lack of consistency in outcomes may be attributable partially to the survivors' age at the initiation of ERT, from a median age of 2.4 months[13] to 4.9 months.[11] Early initiation of ERT may result in a good histologic response[17] and thus a greater benefit to survival compared with late treatment initiation.[10,18] The benefit of early treatment initiation on other outcomes, however, is still unknown.

To achieve early diagnosis and early treatment of IOPD, we initiated a newborn screening (NBS) program for Pompe disease in 2005.[19] By 2011, 10 patients with classic IOPD were diagnosed by NBS, treated with rhGAA, and prospectively monitored at our hospital. All patients were CRIM-positive. With early treatment and little or no antibody interference, this prospective cohort study reveals the outcomes of rhGAA therapy for IOPD.

Methods

The Newborn Screening Center at the National Taiwan University Hospital initiated a NBS program for Pompe disease in 2005. The methods of screening, confirmatory process, criteria for initiating ERT, and follow-up have been described previously.[18,19] Patients with Pompe presenting left ventricular hypertrophy at newborn period were classified as having classic IOPD. Patients with confirmed left ventricular hypertrophy were treated with rhGAA (alglucosidase alfa) immediately, with a dosage of 20 mg/kg every other week. Genomic DNA from peripheral blood cells was used for mutation analysis of the *GAA* gene.[20] CRIM status was determined by western blot analysis.

Survival was compared with a Kaplan-Meier analysis between these patients with NBS, the clinically diagnosed and treated Taiwanese classic IOPD (the clinical cases), and untreated Taiwanese classical IOPD cases (the untreated cases).[18] The clinically diagnosed cases were proven to be CRIM-positive and were treated starting at age 2-6 months because of the presence of clinical symptoms such as respiratory distress or muscle weakness. The untreated cases were archived historically and were not tested for CRIM status. Survival free of ventilation support was defined as the time until invasive ventilation was required or death. Statistical significance was set at $\alpha = 0.05$ (2-tailed).

Other outcome measurements, including the left ventricular mass index (LVMI) measured using 2-dimensional echocardiography,[21] and serum creatinine kinase (CK), were assessed every 3-6 months. Motor development and function evaluation tests, including the Peabody Developmental Motor Scale, Second Edition (PDMS-II)[22] and the Pediatric Evaluation of Disability Inventory specific for Pompe disease (Pompe-PEDI),[23] were conducted every 6 months by 2 experienced therapists. The PDMS-II is a skill-based measure of gross and fine motor development for infants and children from 6 months to 6 years of age; the scores were normalized and are presented as percentiles. The Pompe-PEDI was used to assess the motor capability required for participating in daily locomotion and transfer tasks. The scores of the mobility domain of the Pompe-PEDI Functional Skills Scales, both normative standard scores (adjusted for the child's chronological age) (normal mean = 50, 1 SD = 10) and scaled scores (not adjusted for age), were analyzed in this study. Greater scores reflect a superior capability.

The contribution of other systems, including speech, hearing, vision, and cognition functions, was assessed at least once per year. Facial muscle weakness was defined as an expressionless face with a drooping open or tent-shaped mouth and the absence of the nasolabial folds.[13] Cognitive function was evaluated by the mental development index of the Bayley Scales of Infant Development-II for patients from 1 to 42 months of age and by the cognitive subsets of the Comprehensive Developmental Inventory for Infants and Toddlers[24,25] for patients older than 4 years. All measurements were tested with standardized test materials and procedures, and developmental quotients were derived according to the manuals. Brain magnetic resonance imaging (MRI) scans were performed at baseline and every 1-3 years. Anti-rhGAA IgG antibody titers were monitored every 3-6 months. This prospective observational cohort study was approved by the institutional review board of the National Taiwan University Hospital (NTUH-REC No: 200703045R).

Results

Patients Diagnosed by the NBS Program

During the study period, approximately 470 000 newborns were screened.[26] The overall incidence for Pompe disease was 1 in 17 000, and the incidence for classic IOPD was 1 in 52 000 and for other types was 1 in 25 000.[26] In this study, we included all patients with classic IOPD identified through NBS. In total, 10 newborns were identified during this period. The short-term outcomes of patients 1-5 have been reported.[18] All patients had deficient GAA activity in the lymphocytes/fibroblasts. All patients had at least one allele of the Taiwanese common *GAA* mutation c.1935C>A (p.D645E), which was always associated with the c.1726G>A (p.G576S) pseudodeficiency mutation[27]; this combined mutation is severe, and previous patients who were homozygous for this mutation all had classic IOPD. Thirteen of the 20 mutated alleles of the 10 patients had the c.1935C>A mutation (**Table**). All patients were proven to be CRIM-positive by western blot analysis (data not shown).

The 10 patients were diagnosed at a median age of 9 days (range, 0-33 days). These infants were asymptomatic at the

Table. Detailed clinical data of 10 patients

Patient	Mutation 1	Mutation 2	Age of ERT start (days)	LVMI at baseline/ 6 mo after ERT, g/m^2	Age of independent walk, mo	Current age, mo	Weakness of hip extensors	Hearing loss	Ptosis	Vision	Cognitive function tests	WMH	Titer values maximal/latest
1	c.1935C>A (p.D645E)	c.[1411_1414del; 752C>T; 761C>T] (p.[E471Pfs*5; S251L; S254 L])	26	120/66	14	91	+	M*	–	Astigmatism	91 (CDIIT)	+	12 800/6400
2	c.1935C>A (p.D645E)	c.2842insT (p.L948Sfs*70)	29	170/80	20	90	+	C*	+	Astigmatism	86 (CDIIT)	+	1600/1600
3	c.1935C>A (p.D645E)	c.784G>A (p.E262K)	17	186/67	14	82	+	C*	–		85 (CDIIT)	+	1600/800
4	c.1935C>A (p.D645E)	c.1935C>A (p.D645E)	34	120/71	12.5	76	+	N	–	Myopia	64 (CDIIT)	+	1600/1600
5	c.1935C>A (p.D645E)	c.[1062C>G; 1286A>G] (p.[Y354X; Q429R])	12	109/68	12	72	+	M*	+		89 (CDIIT)	+	6400/800
6	c.1935C>A (p.D645E)	c.1197_1208del (p.V400_N403del)	14	124/84	18	55	+	N	–	Myopia	90 (CDIIT)	NA	200/UD
7	c.1935C>A (p.D645E)	c.2040+1G>T (splicing)	48	70/52	14	51	+	C	–		NA	hypo	3200/800
8	c.1935C>A (p.D645E)	c.1935C>A (p.D645E)	6	168/63	12	34	–	N	+		89 (BSID-II)	N	1600/100
9	c.1935C>A (p.D645E)	c.1935C>A (p.D645E)	14	137/63	15	32	+	N	+		74 (BSID-II)	N	6400/200
10	c.1935C>A (p.D645E)	c.1197_1208del (p.V400_N403del)	16	120/58	20	28	+	C*	–	Myopia	70 (BSID-II)	Hypo	UD/UD

BSID-II, Bayley Scales of Infant Development-II; *C*, conductive hearing loss; *CDIIT*, Comprehensive Developmental Inventory for Infants and Toddlers; *Hypo*, hypomyelination; *M*, mixed type of hearing loss; *N*, normal; *NA*, not analyzed; *Titer*, anti-rhGAA IgG antibodies titer; *UD*, undetectable; *WMH*, white matter hyperintensity.
*With ventilation tube insertion.

time of diagnosis, although 4 presented with feeding-related cyanosis and an enlarged tongue and 3 of them (including patient 7) presented with mild respiratory distress at birth. These 10 patients were treated beginning at a median age of 16 days (6-34 days). At that time all had left ventricular hypertrophy, as assessed by cardiac echography. Patient 7 was diagnosed prenatally because her sister was previously diagnosed with classic IOPD. Patient 7 was born prematurely at 29 weeks of gestation, and she had no obvious cardiomegaly at birth. ERT was initiated at 3 weeks of age when left ventricular hypertrophy was detected and her serum CK levels increased.

Responses to ERT

Survival. The 10 patients were followed and treated with rhGAA for a median duration of 63 months (28-90 months). At the time analysis, all patients survived, remained free of mechanical ventilation, and maintained a normal height and weight at a median age of 63 months (28-91 months). The Kaplan-Meier analysis indicated that the survival of the patients with NBS was significantly better than that of the untreated cases ($P < .001$) or the clinical cases ($P = .028$) (Figure 1, A). Survival free of mechanical ventilation also was markedly better in the NBS group than in both the untreated cases ($P < .001$) and the clinical cases ($P < .001$) (Figure 1, B). One patient (patient 2) was regarded as requiring no mechanical ventilation despite using night-time continuous positive airway pressure as the result of obstructive sleep apnea.

Cardiac Function. The median pre-ERT LVMI was 122 g/m^2 (70-186 g/m^2; normal range <65 g/m^2). Left ventricular hypertrophy improved dramatically during the first 3 months of ERT, resolved in most patients 6 months after ERT initiation (Figure 2; available at www.jpeds.com), and remained stable thereafter.

Serum CK, Motor Development, and Function. The median pre-ERT serum CK level was 827 U/L (109-2406 U/L). The CK levels decreased rapidly during the first 3 months of ERT and reached a nadir (median 255 U/L, range 117-485 U/L) 6 months after ERT initiation (Figure 3, A). All patients demonstrated a delay in achieving head control during early infancy but otherwise attained gross motor milestones in a timely fashion and achieved independent walking at a median age of 14 months (12-20 months) (Table).

Thereafter, their CK levels increased gradually. Their median CK levels were 1032 (492-1700), 1282 (892-1934), 1528 (956-2135), and 1322 (595-2463) U/L at the age of 2, 3, 4, and 5 years, respectively. Their gross motor development, as assessed by the PDMS-II, slowed and lagged further behind the development of age-equivalent normal children over time (Figure 4, A; available at www.jpeds.com). Proximal muscle weakness developed, as evidenced by the appearance of the Gower sign and a waddling gait. Weakness of ankle dorsiflexion also was common. In the mobility domain of the Pompe-PEDI Functional Skills

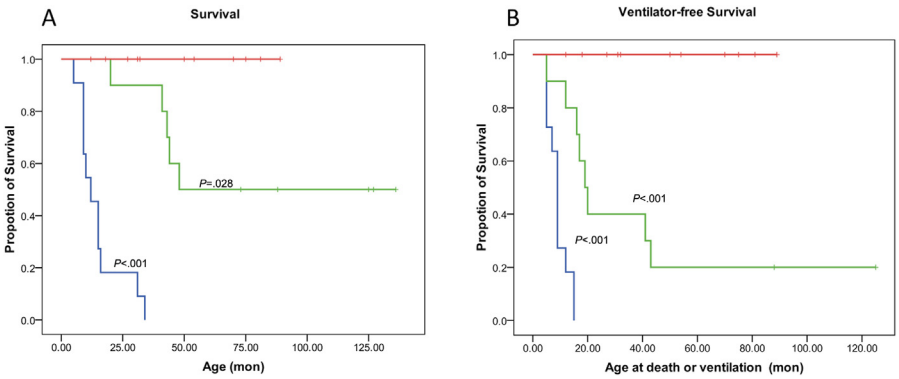

Figure 1. Survival and motor outcomes of patients who were diagnosed by NBS compared with those diagnosed clinically. *Red* represents the screened cases (NBS); *green* represents the clinical cases (clinical cases); and *blue* represents cases from the natural history survey (untreated cases). **A,** Kaplan-Meier survival curve for age at. **B,** Kaplan-Meier survival curve of patients free from ventilation support.

Scales, normative scores declined beginning at an age of 24 months although their scaled scores still increased until an age of 60 months (**Figure 3**, B and C). Therefore, we increased their dosage and frequency of rhGAA infusion to 20 mg/kg/wk or 40 mg/kg/every other week in all 10 patients, and 9 of them continue to have greater dosage/frequency currently (**Figure 5**; available at www.jpeds.com). Our latest policy is to increase dosage/frequency at the age of 2-3 years. At present, it is still too early to evaluate the effects of dose escalation. At the latest follow-up, at a median age of 63 months (28-91 months), all patients could either run or walk fast. Their fine motor development was normal as measured by the PDMS-II (**Figure 4**, B).

Orofacial Manifestations. All patients were fed by mouth without choking as assessed by a speech therapeutist. Abnormal orofacial manifestations included facial muscle weakness (10/10), hypernasal speech (10/10), ptosis (4/10), and hearing loss (6/10) (**Table**). Five patients had tubes inserted for otitis media with effusion, and 3 patients (3/10) had myopia that needed correcting.

Brain Manifestations and Cognitive Function. The cognitive function scores of the study patients are shown in the **Table**. Most patients had normal scores at the age of 12 months but became slightly impaired at the age of 24 months; however, the scores seemed to improve thereafter (**Figure 6**; available at www.jpeds.com). Patient 7 was uncooperative during the last assessments at the age of 48 months. The lower developmental quotients in patient 4 could be attributable to low social economic status. MRI studies occasionally have found hypomyelination in newborns, but this finding resolved before 1 year of age. MRI studies at an older age, however, revealed white matter abnormalities in 7 of the 9 patients who had MRI scans. These abnormalities include T2-weighted hyperintense signals in the white matter of 5 patients (**Figure 7**) and hypomyelination in 2 patients. Longitudinal studies in patients revealed that the T2-weighted hyperintensity increased with time, but the areas of involvement did not enlarge. Currently, the oldest 4 patients (patients 1-4) have attended regular elementary schools at appropriate ages, although 3 (patients 1, 2, 4) needed additional classes for Chinese language and 2 (patients 1 and 2) needed additional classes for mathematics.

Antibody Status

Because all patients harbored at least one c.1935C>A mutation, which is associated with residual GAA protein and predicts CRIM-positive status, we didn't initiate immune tolerance induction treatment before the first exposure of rhGAA. Patients had no anti-rhGAA IgG antibodies before treatment. Nine patients developed detectable anti-rhGAA IgG antibodies during treatment. The mean time to developing detectable antibody was 7.6 months (median 3 months, range 1-50 months). For all 10 patients, the mean peak titer was 3540 (median 1600, range 0-12 800). The high maximal titers appeared in patient 1 and persisted for 13 months. The mean last titer was 1230 (median 800, range 0-6400). These results demonstrate a downward trend over time in median anti-rhGAA IgG antibody titers. Overall, our patients had low anti-rhGAA IgG antibody titers (greatest was equal to 12 800); no patient had high sustained antibody titers.

Discussion

This study demonstrates better outcomes of classic IOPD in all the domains that we measured. The 10 patients identified by NBS were treated with rhGAA since birth (median 16 days, range 6-34 days). These patients had deficient GAA activity, 2 severe mutations, and left ventricular hypertrophy shortly after birth, consistent with the severe phenotype of IOPD. In comparison with previously reported patients with CRIM-positive IOPD, our treatment results are significantly better in survival, mechanical

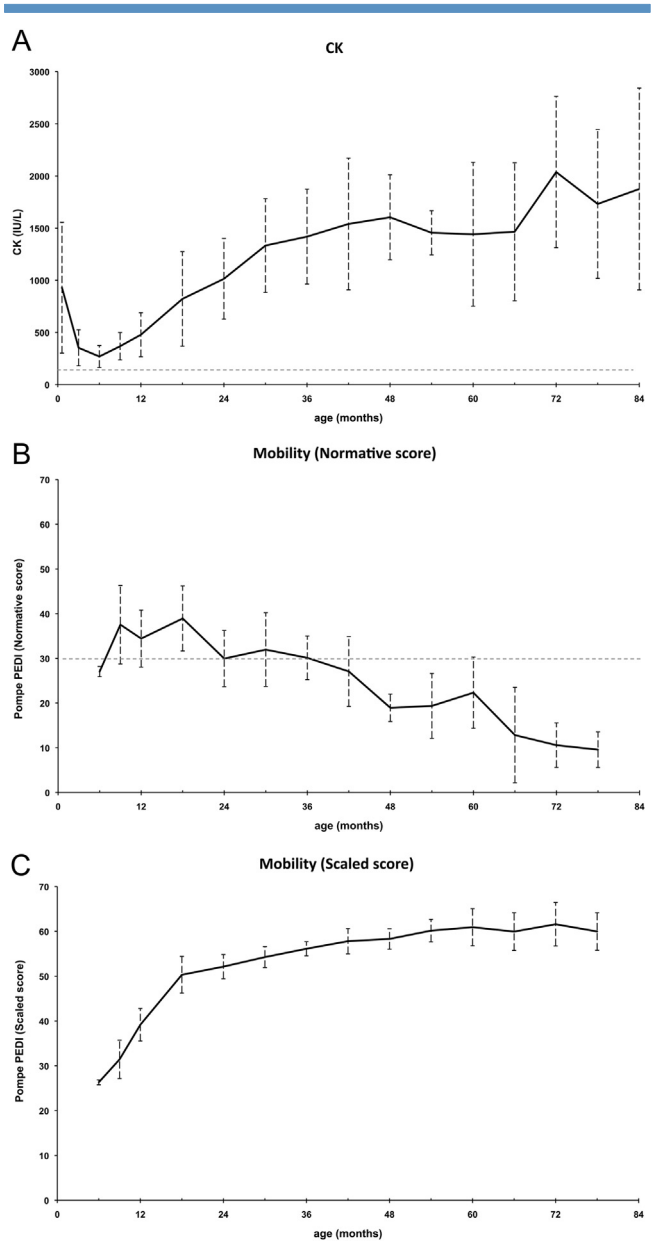

Figure 3. Change of serum CK and motor function of patients diagnosed by NBS. **A,** Mean CK levels (normal range 38-160 U/L; the *gray dashed line* indicates the upper limit of 160 U/L). **B,** Mean normative and **C,** scaled scores of Functional Skills Scales of Mobility scores of the Pompe-PEDI. Normal mean of normative scores = 50, 1 SD = 10; the *gray dashed line* indicates the lower limit of 2 SD, which is 30. Greater scores reflect superior capability.

ventilator-free survival, motor development, and life quality. Our patients have a 100% survival and remained free of mechanical ventilation, and ventilator-free survival decreased to less than 50% in the clinical trial data. All our patients walked or ran independently, and few patients in previous reports could do that. We followed our patients longitudinally and presented quantitative motor function data. Moreover, all of our patients attend standard schools at appropriate ages, which indicates their good life quality compared with most patients in other reports. This is the first and the largest prospective study of patients with classic IOPD (CRIM-positive) treated since birth. The improvement of outcomes in our cohort compared with previous reports[11,13,28] should be largely the result of early treatment initiation. The result of the present study proves that rhGAA therapy for classic IOPD is effective if the treatment can be initiated shortly after birth.

Despite an initial decrease in CK levels and excellent morphology of muscle biopsies after 6 months of ERT,[18] weakness of the truncal muscles occurred early in these early-treated patients, as evidenced by their delay in achieving head control and inability to sit up from the supine position. A slow decrease in motor function caused by proximal muscle weakness then occurred and was associated with an increase in CK levels, starting at 18-24 months of age. Elevation of CK levels usually suggests muscle damage, and studies in mice have demonstrated the inability of ERT to clean glycogen storage from the skeletal muscles.[29] Reasons for this possible shortcoming of rhGAA in proximal muscles include the differential expression of the angiotensin-converting enzyme gene,[30] autophagy buildup,[31] poor drug internalization,[32] low expression of mannose-6-phosphate receptors,[33] or epigenetic and environmental factors.[34] We have attempted to increase the dosage and frequency of rhGAA infusion to evaluate whether muscle function can be improved, but it is still too early to evaluate the effects.

Neurogenic involvements also may contribute to the symptoms in these early-treated patients. Glycogen accumulation has been demonstrated in both the anterior horn neurons of the cervical spinal cord[35] and the brainstem neurons of patients with Pompe disease.[36] Impairments of these motor neurons may impair respiratory, swallowing, and speech functions. Brain dysmyelination also has been observed in late-treated patients with classic IOPD,[14,16,37] and now in the early-treated patients. The follow-up period, however, is short, so it is not possible to draw long-term conclusions, and the relationship between MRI findings and cognition is unclear at this point.

Speech disorders cause difficulty in oral communication in our patients. The flaccid dysarthria in Pompe disease can be attributable to myogenic or neurogenic involvement.[38] We recently demonstrated severe glycogen accumulation in the eye levator muscle of a patient who had an excellent response to ERT in his quadriceps muscle.[39] Therefore, it is possible that glycogen storage in the muscles involving speech cannot be prevented by early treatment. Alternatively, glycogen storage in the brainstem motor neurons could impair the function of cranial nerves that control the oral, facial, laryngeal, and pharyngeal muscles. The reduced sensitivity of the larynx and pharynx and the delayed swallowing in treated patients with IOPD indicates brainstem dysfunction,[13] likely caused by glycogen accumulation in the motor neurons of the brainstem in Pompe disease.[35,40] Because rhGAA cannot enter the brain, neurogenic involvement in Pompe disease will not be resolved with ERT. Either an enhancement in ERT, especially to muscles[41] such as the bulbar muscles, or a treatment that

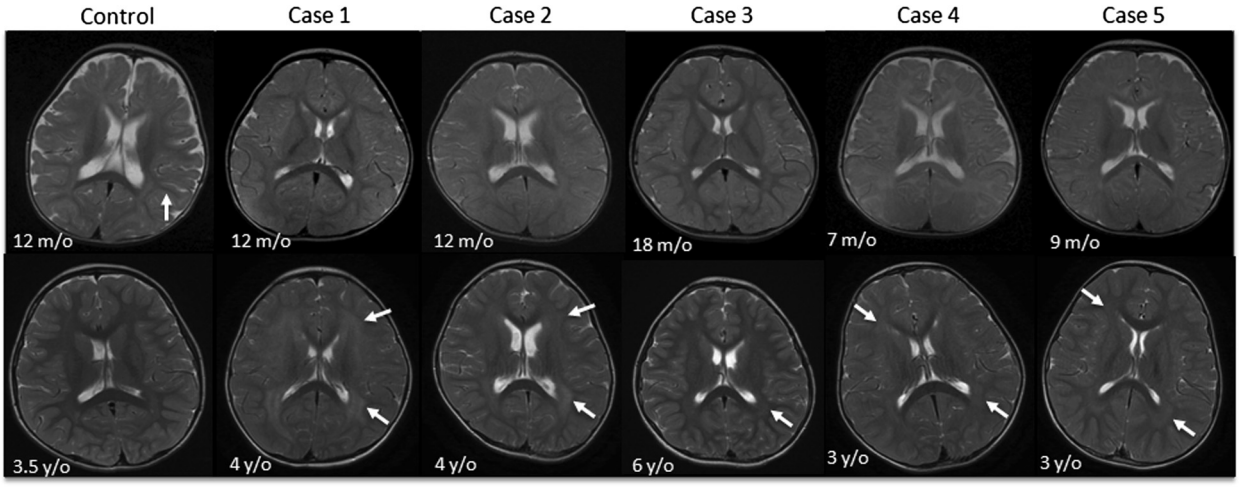

Figure 7. Brain MRIs from 1 control subject and 5 patients. The *upper panel* shows the results of the MRI study with children at young ages (age 7-18 months). Normal myelination, represented by the *white* signal in the T2-weighted images, has reached the cortex in the control subject (*arrow*), but all 5 patients showed signs of hypomyelination. The *lower panel* shows the results of MRI studies performed with children at older ages (3-6 years). Myelination in the subcortical areas has improved in patients with Pompe, but hyperintensity (*arrows*) in deep white matter was seen in all 5 patients.

targets the neurons may be able to clarify this etiology and further improve patients' outcomes.

Pompe disease is rare and our case number is too small to do subgroup analysis, such as genotype-phenotype correlations. The variation in the parents' socioeconomic status confounded the cognitive function analysis of the patients. Only one evaluator was responsible for each patient because data consistency is critical in longitudinal studies. Therefore, the evaluations were not blinded, which decreased the objectivity of the study. This study only involved patients who are CRIM-positive. Immune modulation therapy is required for patients who are CRIM-negative to prevent the interference of antibodies,[42] and immune tolerance induction[43] should be performed before the first exposure of rhGAA.

We have presented the uniformly positive responses of patients identified by NBS who have been treated with rhGAA since birth for a period of 28-90 months. They experienced long-term survival without requiring ventilation and nearly normal development but presented with residual myopathy and other manifestations such as ptosis and speech disorders. Antibodies frequently impair outcomes in patients who are CRIM-negative, but in this study even with little or no antibody interference, patients still had residual deficits. Further adjuvant therapies, both targeted to the muscles and to the neurons, will be needed to further improve clinical outcomes. ■

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Reprint requests: Wuh-Liang Hwu, MD, PhD, Department of Pediatrics and Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan. E-mail: hwuwlntu@ntu.edu.tw

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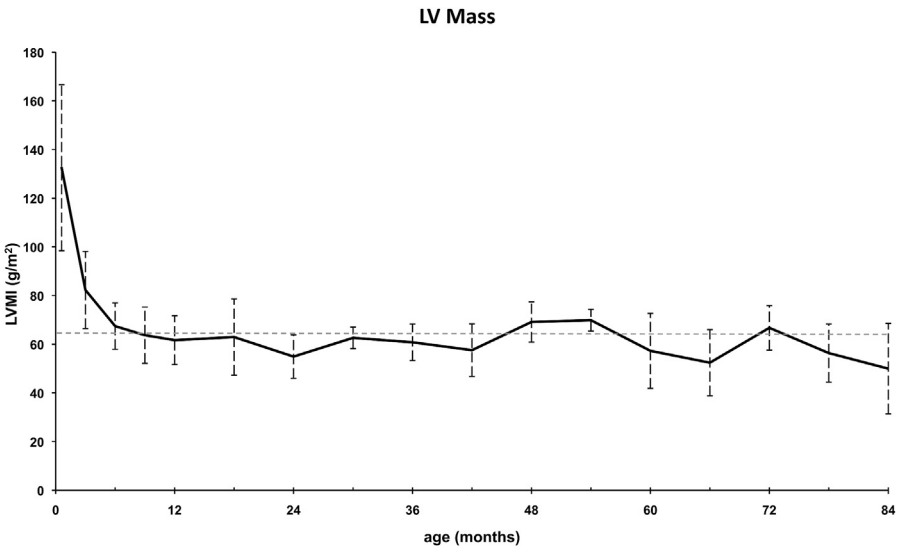

Figure 2. Mean LVMI from baseline through the present for patients diagnosed by NBS. Normal range <65 g/m^2 (*dashed line*). *LV*, left ventricle.

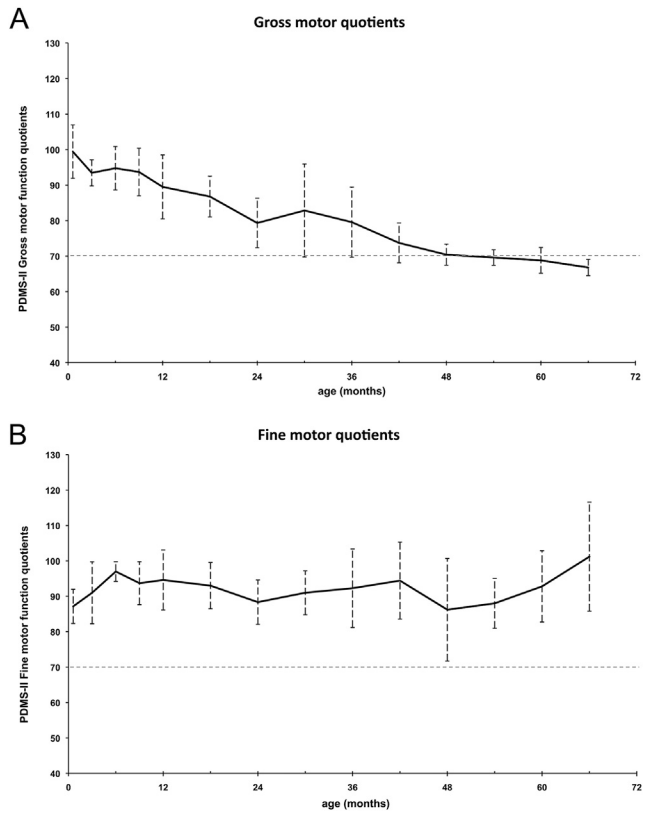

Figure 4. Motor development in patients diagnosed by NBS was evaluated by the PDMS-II. The scores were normalized and presented as quotients (Normal mean = 100, 1 SD = 15). **A,** Mean gross motor quotient (the *gray dashed line* indicates the lower limit of 2 SD, ie, 70). **B,** Mean fine motor quotient (the *gray dashed line* indicates the lower limit of 2 SD, ie, 70).

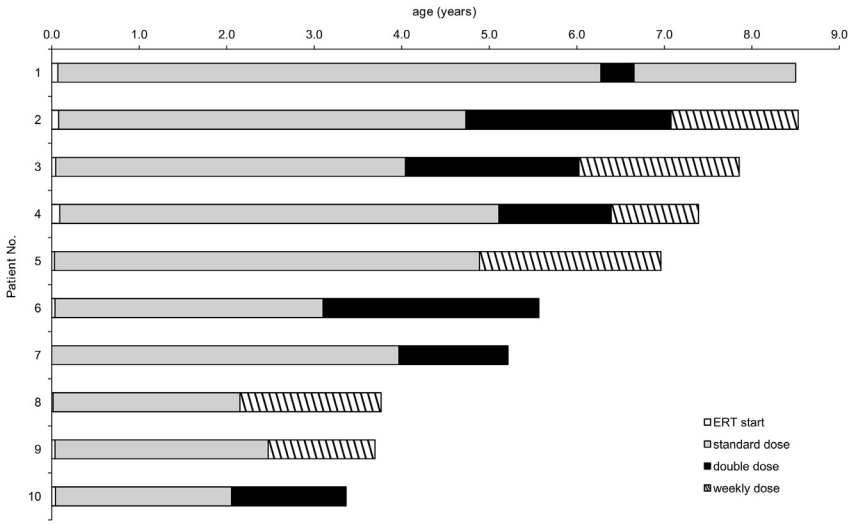

Figure 5. Dose and frequency of rhGAA infusions in patients diagnosed by NBS. Most of the patients now receive greater or more frequent dosing than the label dose of 20 mg/kg every other week.

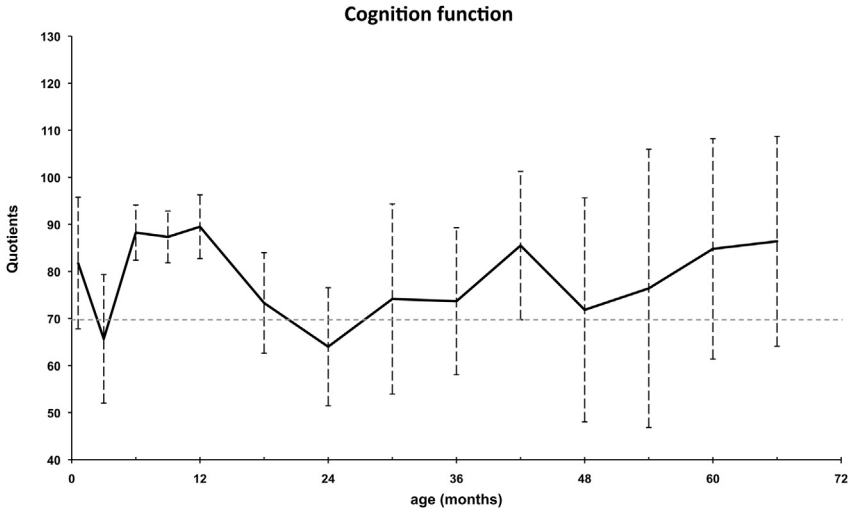

Figure 6. Cognitive functions in patients diagnosed by NBS were evaluated by the cognitive subsets of the Comprehensive Developmental Inventory for Infants and Toddlers for patients older than 4 years and by the mental development index of the Bayley Scales of Infant Development-II for patients between one and 42 months of age. The scores were normalized and are presented as quotients (normal mean = 100, 1 SD = 15; the *gray dashed line* indicates the lower limit of 2 SD, ie, 70).