RESEARCH ARTICLE

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A Large-Scale Nationwide Newborn Screening Program for Pompe Disease in Taiwan: Towards Effective Diagnosis and Treatment

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The aim of this study was to: (a) analyze the results of a large-scale newborn screening program for Pompe disease, and (b) establish an effective diagnostic protocol to obtain immediate, valid diagnosis of infantile-onset Pompe disease (IOPD) to promote earlier treatment and better outcomes. In this study, 402,281 newborns were screened for Pompe disease from January 1, 2008 to May 1, 2012. Infants with low acid α-glucosidase (GAA) activity were referred to Taipei Veterans General Hospital for diagnostic confirmation. Physical examination, biochemical parameter (creatine kinase [CK], alanine transaminase, aspartate aminotransferase, and lactate dehydrogenase), and echocardiogram assessments were performed immediately to effectively differentiate IOPD from suspected late-onset Pompe disease (LOPD) or false-positive cases with pseudodeficiency mutation. Six infants with IOPD all presented with hypotonia, extremely low GAA enzyme activity (≤0.5 μmol/L/hr) in initial dried blood spot analysis, high CK (≥250 U/L), and high left ventricular mass index (LVMI, ≥80 g/m^2). By analyzing these parameters, IOPD was distinguished effectively and immediately from suspected LOPD and false-positive cases. Except for the first referred case, five of the infants with IOPD received first-time enzyme replacement therapy (ERT) within 4 hr of admission and exhibited marked improvement. Our findings indicate that certain clinical manifestations (hypotonia, high CK, enlarged LVMI, and extremely low GAA enzyme activity in initial dried blood spot analysis) can help in the rapid and effective differentiation of patients with IOPD from other patient with low GAA activity. Such differentiation allows for the early application of first-time ERT and leads to better outcomes.

Key words: infantile-onset Pompe disease; acid α-glucosidase; enzyme replacement therapy; newborn screening

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INTRODUCTION

Pompe disease, which is also called glycogen storage disease type II and acid maltase deficiency [Hirschhorn and Reuser, 2001], was first described by Pompe [1932]. It is a rare, autosomal recessive disorder caused by a deficiency of acid α-glucosidase (GAA) [Pompe, 1932]. Pompe disease has a worldwide incidence of approximately one in 40,000 individuals [Pompe, 1932; Lin and

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Shieh, 1996]. The most severe form, infantile-onset Pompe disease (IOPD), is characterized by progressive cardiac hypertrophy, hypotonia, respiratory distress, and delayed motor development [van den Hout et al., 2003; Kishnani and Howell, 2004]. Diagnosis of IOPD is usually delayed by 3 to 6 months, with only approximately 8% of children surviving beyond 1-year without treatment [Kishnani and Howell, 2004; Kishnani et al., 2006]. Late-onset Pompe disease (LOPD) has a wide spectrum of symptoms characterized by myopathy and respiratory insufficiency, although the cardiac muscle is usually not involved [Müller-Felber et al., 2007; Chien et al., 2008; Wokke et al., 2008; van der Ploeg et al., 2010; Reuser et al., 2011]. In the absence of obvious clinical symptoms at disease onset, patients with LOPD can remain undiagnosed for years.

In 2006, enzyme replacement therapy (ERT) was approved for the treatment of Pompe disease. Data from clinical trials have shown that ERT can prolong ventilator-free survival and motor function [Müller-Felber et al., 2007; Wokke et al., 2008; van der Ploeg et al., 2010; Reuser et al., 2011]. However, to provide better outcomes, ERT should be initiated before irreversible muscle damage [Chien et al., 2009; Kishnani et al., 2009; Nicolino et al., 2009; Spiridigliozzi et al., 2011; Case et al., 2012]. Indeed, even when the age at diagnosis of IOPD is less than 2 months, obvious hypotonia, myopathy, cardiac hypertrophy, and some irreversible muscle damage may have occurred [Müller-Felber et al., 2007; Chien et al., 2008; Wokke et al., 2008; van der Ploeg et al., 2010; Reuser et al., 2011]. Therefore, infants diagnosed with IOPD should receive ERT as early as possible to prevent permanent muscle damage.

Measurement of GAA activity by analyzing a dried blood spot (DBS) on filter paper using fluorescence assay or tandem mass spectrometry is a method that is readily available and can be used for nationwide newborn screening and the early identification of IOPD [Kishnani et al., 2009]. Taiwan has established a nationwide newborn screening program for Pompe disease, which has operated successfully since 2005 [Chien et al., 2008]. Currently, more than 90% of newborns are screened for Pompe disease. Approximately two-thirds of samples are evaluated by the Taipei Institute of Pathology and The Chinese Foundation of Health neonatal screening center. Newborns with positive results are then referred to Taipei Veterans General Hospital for diagnostic confirmation. Since 2008, Taipei Veterans General Hospital has become one of the major institutions for identifying and treating Pompe disease in Taiwan [Chien et al., 2008, 2009]. From January 1, 2008 to May 1, 2012, a total of 402,281 infants were screened and seven infants were diagnosed with IOPD. The volume of available data encouraged us to share the results of our screening program.

According to our experience, it takes around 10–30 days to acquire the results of genetic studies, muscle biopsies, and lymphocyte enzyme assays to confirm the diagnosis of Pompe disease. Therefore, determining how to facilitate earlier diagnosis would be of obvious benefit with regards to the initiation of prompt and effective treatment. In the present study, we tried to identify patients with IOPD by analyzing clinical manifestations, basic biochemical parameters, and echocardiography findings. All of these tests/procedures can be completed within 2 hr of patient admission.

In this article, we describe the results of an extensive newborn screening program for Pompe disease, how we effectively recognized IOPD, and discuss our experience treating and following six patients with IOPD over a 4-year period.

METHODS

Study Design and Sample

This study involved 402,281 newborn infants who were screened as part of a nationwide screening program in Taiwan from January 1, 2008 to May 1, 2012. The newborn screening program for Pompe disease was integrated into the Taiwan newborn screening system, and informed consent was obtained for each sample collected. Taipei Veterans General Hospital began to evaluate approximately two-thirds of newborns from January 1, 2008.

Screening Algorithm

Infants born at participating hospitals during the study period were screened. Peripheral blood samples for the DBS screening tests were collected within 3 days of birth. Testing of the samples was conducted at the Taipei Institute of Pathology and The Chinese Foundation of Health neonatal screening center using fluorescence assay or tandem mass spectrometry (after October 2010). Infants with GAA activity $\leq$0.50 μmol/L/hr (normal reference, >2.0 μmol/L/hr) were immediately referred to Taipei Veterans General Hospital for diagnostic confirmation. When GAA activity was 0.51 to 1.60 μmol/L/hr, the central labs called for a second DBS specimen. If the second GAA activity level was $\leq$0.50 μmol/L/hr, infants were referred to the hospital. If the second GAA activity level was found to be between 0.51 and 1.00 μmol/L/hr, a third test was run. If the third GAA activity level was $\leq$1.00 μmol/L/hr, infants were referred to the hospital.

Evaluation and Diagnostic Confirmation

Physical examinations, blood sampling, and echocardiography were performed immediately upon referral of infants. Blood samples were assessed for creatine kinase (CK), alanine transaminase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) levels, lymphocyte GAA enzyme activity, and GAA gene sequencing. Quadriceps muscle biopsies were taken after parental informed consent was obtained. Specimens were used for high-resolution light microscopy with periodic acid-Schiff (PAS), hematoxylin and eosin (H&E) staining, and electron microscopic examination.

ERT was started immediately upon confirmed diagnosis of IOPD. Intravenous alglucosidase alfa (Myozyme®, Genzyme Corp., Cambridge, MA) 20 mg/kg was given bi-weekly. All patients with IOPD underwent a physical therapy regimen, including extremity and trunk muscle strength training, exercises to enhance head support from prone and supine positions, exercises to assist with sitting and standing, and oropharyngeal exercises every 2 weeks when they were admitted for regular ERT. Echocardiography was performed every month for 6 months and then every 3 to 6 months. Blood chemistry tests for CK, LDH, ALT, and AST were performed monthly for 6 months and then every 3 months. In addition,

periodic developmental surveys were conducted using the Peabody Developmental Motor Scale, Second Edition (PDMS-II) [Folio and Fewell, 2000], a skill-based measure of gross and fine motor development from 6 months to 6 years of age, and the Alberta Infant Motor Scale (AIMS), an observational measure of infant motor performance from birth to the age of independent walking [Piper et al., 1992].

LOPD was suspected upon detection of two distinct LOPD-related GAA gene mutations or one LOPD-related GAA gene mutation combined with one IOPD-related mutation from the whole sequence gene study [Kumamoto et al., 2009; Labrousse et al., 2010; Shigeto et al., 2011]. Pseudodeficiency was indicated by a homozygous pseudodeficiency mutation (c.1726G > A, p.G576S) or one pathogenic mutation combined with pseudodeficiency mutation of at least one allele. Note: pseudodeficiency mutation has been associated with low GAA activity not related to Pompe disease [Kumamoto et al., 2009; Labrousse et al., 2010; Shigeto et al., 2011].

Statistical Analysis

Data are presented as median with interquartile range. GAA activity, CK, LDH, AST, ALT, and LVMI were compared between patients with IOPD, suspected LOPD or pseudodeficiency by Kruskal–Wallis test. All statistical assessments were two-sided and evaluated at the 0.05 level of statistical significance. Statistical analyses were performed using SPSS 15.0 statistics software (SPSS Inc., Chicago, IL) and SigmaStat 3.1 (Jandel Scientific, San Rafael, CA).

RESULTS

The screening algorithm and results of screening are shown in Figure 1. Among 402,281 infants screened, 321 who screened positive for low GAA activity by DBS were referred to Taipei Veterans General Hospital. A total of seven patients were confirmed to have IOPD. One of these patients was referred to another hospital for diagnostic confirmation because her older sister, who also had IOPD, had received regular ERT at that hospital. Six infants with IOPD were diagnosed and received ERT at our hospital. Also identified were 20 cases of suspected LOPD and 294 cases of pseudodeficiency.

The demographic characteristics of the six patients with IOPD are presented in Table I. Age at presentation ranged from 9 to 52 days. All were born to healthy, nonconsanguineous parents. All six patients were cross-reactive immunologic material (CRIM) positive and exhibited all of the following manifestations: general weakness and feeding difficulty, extremely low GAA activity ($\leq$0.50 μmol/L/hr), elevated CK ($\geq$250 U/L), and elevated LVMI ($\geq$80 g/m^2). Muscle biopsy results for all six patients revealed

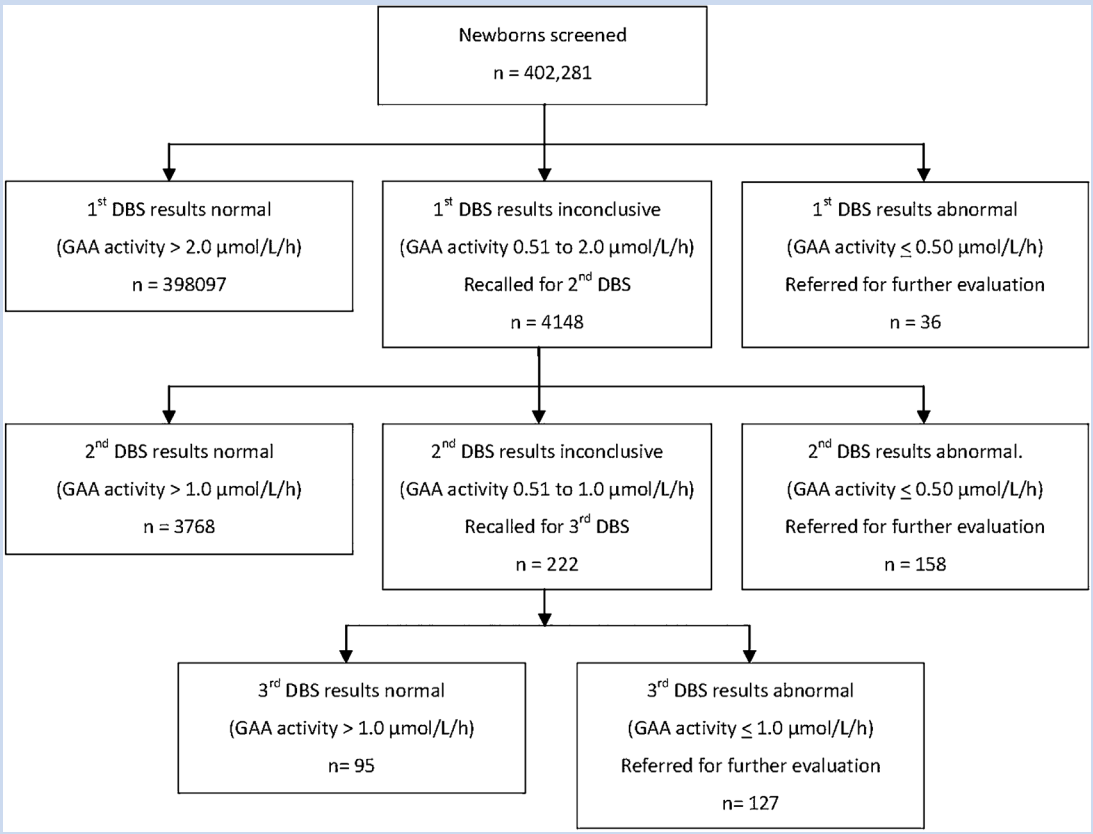

FIG. 1. Flow chart of screening algorithm.

TABLE I. Patient Characteristics

Case #	Sex	GA (weeks), BBW (kg)	Age at referral (days)	Age at first ERT (days)	Symptoms at diagnosis	GAA activity (μmol/L/hr)	CK (U/L)	LDH (U/L)	AST (U/L)	ALT (U/L)	LVMI (g/m^2)	GAA mutation
1	F	38, 3.1	51	79	Mild hypotonia, Feeding difficulty, Macroglossia	0.10	279	443	147	82	190.0	c.1935C → A, (p.D645E), homozygous
2	F	37, 3.2	18	18	Mild hypotonia, Feeding difficulty, Macroglossia	0.22	591	579	108	44	81.6	c.1411_1414del, (E471fsX5), heterozygous c.872T → C, (p.L291P) heterozygous
3	M	38, 3.5	15	15	Mild hypotonia, Macroglossia	0.36	542	533	114	48	154.2	c.1935C → A, (p.D645E), homozygous
4	M	39, 3.3	9	9	Mild hypotonia, Macroglossia	0.15	662	555	113	45	110.2	c.1935C → A, (p.D645E), heterozygous c.2303C → T, (p.P768L), heterozygous
5	M	38, 3.1	12	12	Mild hypotonia, Macroglossia	0.13	443	716	146	50	104.9	c.1396G → T, (p.V466F), heterozygous c.1935C → A, (pD645E), heterozygous
6	M	39, 3.0	9	9	Mild hypotonia, Macroglossia	0.04	766	646	145	51	191.5	c.1935C → A, (p.D645E), homozygous

GA, gestational age; BBW, birth body weight; GAA, acid alpha-glucosidase; CK, creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LVMI, left ventricular mass index; F, female; M, male.
Reference levels: GAA activity ≥2 μmol/L/hr; CK<170 U/L male, <240 U/L female; LDH 170–580 U/L; AST 15–60 U/L; ALT 5–28 U/L; LVMI 47.4 ± 6.2 g/m^2.

TABLE II. Biochemical Parameters of Screened Patients

	IOPD (n = 6)		Suspected LOPD (n = 20)		Pseudodeficiency (n = 294)		*P*-value*
Parameter	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**	
CK, U/L	566	279–766	72†	37–119	78†	25–233	<0.0001
LDH, U/L	567	443–716	258†	235–350	298†	151–476	<0.0001
AST, U/L	129.5	108–147	31†	23–77	33†	14–114	<0.0001
ALT, U/L	76	44–82	31†	14–74	22†	9–71	<0.0001
LVMI, g/m^2	132.2	81.6–191.5	41.4†	31.9–55.2	40†	29.3–72	0.0011
GAA activity, μmol/L/hr	0.16	0.04–0.36	0.65†	0.10–1.66	1.04†	0.06–2.00	<0.0001

IOPD, infant-onset Pompe disease; LOPD, late-onset Pompe disease; CK, creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LVMI, left ventricular mass index; GAA, acid α-glucosidase.
P-value is significant at <0.05.
*Kruskal–Wallis test, comparing all 3 groups.
†Mann–Whitney U test, compared to IOPD group.

significant involvement of muscle fibers. On H&E staining, most sections showed severe vacuolization of myocytes. Electron microscopy revealed accumulation of lysosomal glycogen in most cells. Myofibrils were completely replaced by cytoplasmic glycogen. Analysis of PAS-stained sections revealed variable amounts of glycogen in most skeletal myocytes.

Biochemical and echocardiographic data (GAA activity, CK, LDH, AST, ALT, and LVMI) are summarized in Table II and Figure 2. There were significant differences among the IOPD group and suspected LOPD and pseudodeficiency groups for all parameters (all $P < 0.05$). In patients with IOPD, GAA activity was extremely low (median: 0.15 μmol/L/hr [range: 0.01–0.36 μmol/L/hr], CK was elevated (median: 566 U/L [range, 279–766 U/L]), and LVMI was elevated (median: 132.2 g/m^2 (range: 81.6–191.5 g/m^2). There were no significant differences in the parameters between the suspected LOPD and pseudodeficiency groups.

The first referred case (Patient 1) was referred at 51 days of age. This patient received ERT at 79 days after diagnosis was confirmed by muscle biopsy, lymphocyte GAA enzyme assay, and GAA gene sequencing. For Patients 2–6, ERT was initiated within 4 hr of hospital admission at 9–18 days of age.

Changes in CK, LDH, AST, ALT, and LVMI over time are presented in Figure 3. CK, LDH, AST, and ALT showed marked rapid decreases in the 6 months after the initiation of ERT, followed

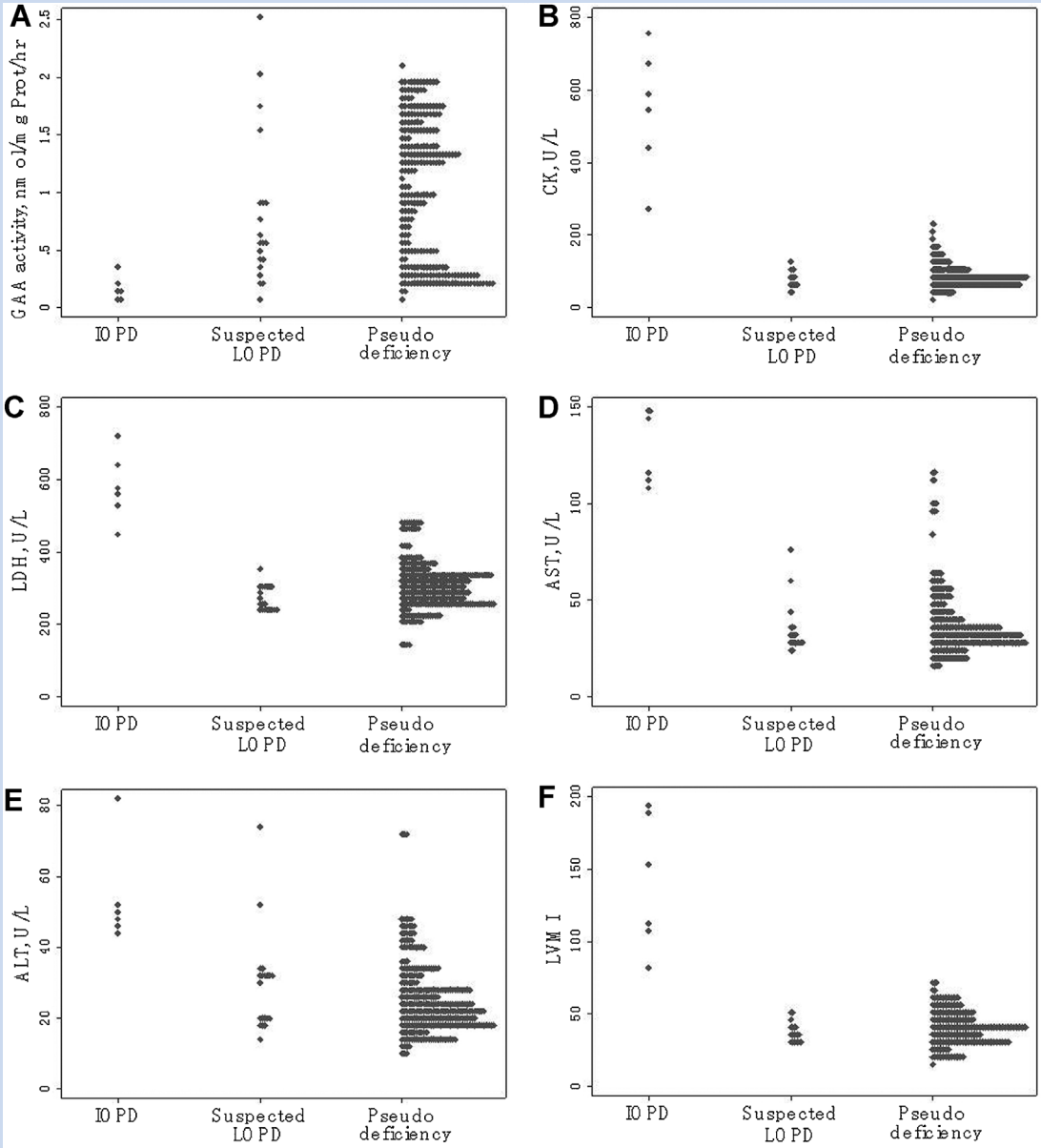

FIG. 2. Dot plot of acid α-glucosidase (GAA) activity (A), creatine kinase (CK) (B), lactate dehydrogenase (LDH) (C), aspartate aminotransferase (AST) (D), alanine transaminase (ALT) (E), and left ventricular mass index (LVMI) (F) for infants with low GAA activity in dried blood spot samples.

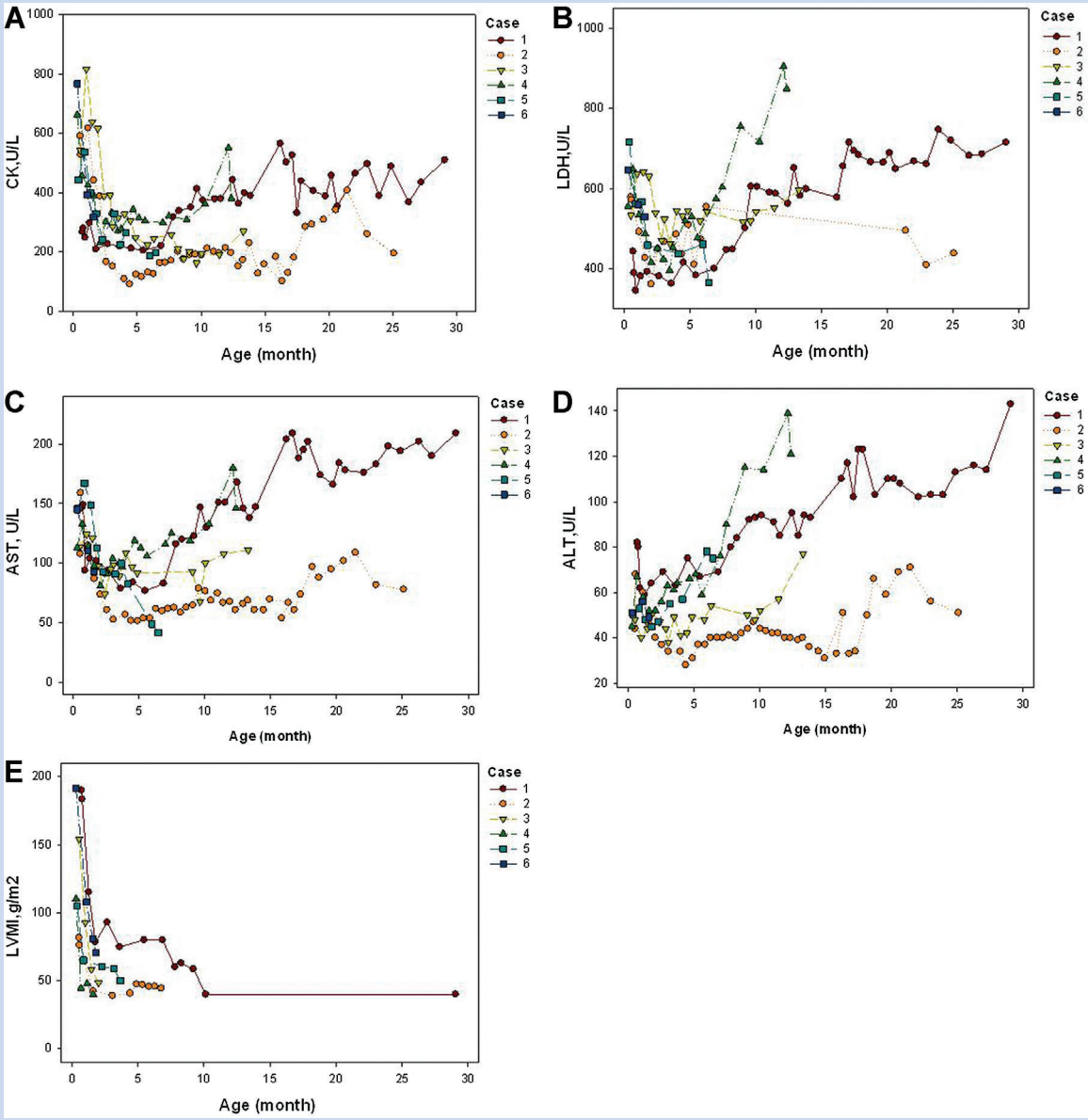

FIG. 3. Change in creatine kinase (CK) (A), lactate dehydrogenase (LDH) (B), aspartate aminotransferase (AST) (C), alanine transaminase (ALT) (D), and left ventricular mass index (LVMI) (E) for the six patients with infantile-onset Pompe disease.

by gradual increases over time (Fig. 3A–D). The increase over time may result from increasing activity or perhaps, to some extent, due to sustained skeletal myocyte damage caused by accumulation of material in lysosomes. Cases 2–6 demonstrated rapid, dramatic decreases in LVMI within 2 months after receiving regular ERT. However, in Case 1, the rate of LVMI decrease was notably slower compared with the other cases. In this case, LVMI was normalized approximately 10 months after the start of ERT (Fig. 3E).

Before ERT, patients with IOPD exhibited hypotonia, especially with regards to head and jaw control. AIMS assessments showed significant motor developmental delay. After regular ERT, most patients showed improvement in motor skills as indicated by improved AIMS and PDMS-II scores. Of note, the time to normalization of PDMS-II scores in Patients 1 and 3, both of whom had the same mutation (c.1935C → A, [p.D645E], homozygous) was quite different; 14 months in Patient 3 versus 27 months in Patient 1.

At most recent follow-up, all six patients diagnosed with IOPD were healthy, with normal respiratory and cardiac function, and improved muscle control and trunk strength. None of the patients required a wheelchair or walking device at any time during the observation period.

DISCUSSION

The present study is one of the largest series to date to report on newborn screening for Pompe disease. In our series of 402,281

infants screened for Pompe disease, 321 with low GAA activity were referred to Taipei Veterans General Hospital. Among these, seven infants were diagnosed with IOPD. Six of these infants received regular ERT at our hospital, five of six within 4 hr of admission.

Our results indicate that the prevalence of IOPD in Taiwan is 0.0017% (1/57,000). This prevalence is lower than previously reported in Taiwan [Lin and Shieh, 1996], but is similar to other national reports [Meikle et al., 1999; Pinto et al., 2004; Kemper et al., 2007; Oda et al., 2011].

Newborn screening for Pompe disease has been shown to be feasible in Taiwan and other countries [Kemper et al., 2007; Chien et al., 2008; Chien et al., 2009; Oda et al., 2011]. In this study, several parameters were analyzed for the confirmation of IOPD: hypotonia with extremely low GAA activity in the initial DBS (<0.50 μmol/L/hr), elevated CK (>250 U/L), and elevated LVMI (>80 g/m^2). All of our patients with IOPD who simultaneously exhibited all of these characteristics could be clearly distinguished from patients with suspected LOPD or pseudodeficiency. In our series, using this diagnostic protocol for IOPD, the positive and negative predictive values were both 100%.

Similar to patients in our large-scale study of Pompe disease, patients with IOPD in other large studies also exhibited obvious hypotonia, high CK, and significantly elevated LVMI [Chien et al., 2008, 2009; van Capelle et al., 2010; Bonilla-Palomas et al., 2012]. In the other studies, GAA activity was measured in the initial DBS using different assays [Chien et al., 2008, 2009; van Capelle et al., 2010; Bonilla-Palomas et al., 2012]; hence, the cut-off point for extremely low GAA activity must be set according to the assay. However, according to our data, even though patients with IOPD had very low GAA activity, there were still some overlap with cases of suspected LOPD and false-positive cases. Therefore, using our diagnostic protocol, combining clinical presentation, CK, and LVMI data, patients with IOPD could be effectively distinguished from other cases. Although our results were significant, the number of patients was small and an exception may have occurred in our ongoing program. Nevertheless, our protocol was still helpful for identifying likely patients with IOPD after abnormal newborn screening results.

Initiating ERT before significant irreversible muscle damage is critical for improving outcomes in patients IOPD [Chien et al., 2008; van Capelle et al., 2010]. Comparing the risks and benefits of early ERT for patients with highly suspected IOPD, the benefits of ERT outweigh the low risk of adverse effects [Oda et al., 2011]. Patients 2–6 in our study all demonstrated a reduction in LVMI within 2 months of starting ERT. This timing of reduction is faster than previously reported [van den Hout et al., 2003; Kemper et al., 2007; Chien et al., 2008, 2009; Oda et al., 2011]. Early identification of suspected IOPD promotes initiation of early treatment and facilitates better outcomes [Chien et al., 2011].

The allele frequency of the pseudodeficiency allele p.G576S in the Taiwanese population is 14.5% [Labrousse et al., 2010]. The high prevalence of the pseudodeficiency mutation complicates the differentiation of IOPD by GAA activity alone. Applying our reliable diagnostic protocol that combines clinical presentation, CK, and LVMI data, allows for earlier detection and treatment of patients with IOPD.

In our study, there were significant differences in CK levels between patients with IOPD and other patients. In our institution, biochemical parameters and echocardiography can be carried out and the results confirmed within 2 hr. Therefore, Patients 2–6 were able to receive first-time ERT within 4 hr after they were admitted to our hospital. In Patient 1, first-time ERT was delayed until diagnosis was confirmed by muscle biopsy, lymphocyte GAA enzyme activity, and GAA gene sequencing. As a consequence, the rate of decrease in LVMI over time was slower than that observed in the other cases where ERT was initiated earlier. The follow-up program is ongoing for our patients with IOPD. It is anticipated that further data will be generated to assess the longer term prognoses of patients who receive early ERT.

Our study has several limitations that warrant mention. Although our results were generally favorable, the number of treated patients was small and the length of follow-up was limited. The long-term clinical status of our patients remains unknown, and longer follow-up is essential to investigate sustainable outcomes in adults.

CONCLUSIONS

In conclusion, the results of our study indicate that newborn screening for Pompe disease and application of a reliable diagnostic protocol can promote effective, timely detection of IOPD, and can facilitate early initiation of first-time ERT. We suggest that adopting the diagnostic strategy used in this study allows earlier diagnosis and expedited initiation of treatment, which may lead to better outcomes for patients with IOPD.

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