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The Natural Course of Infantile Pompe's Disease: 20 Original Cases Compared With 133 Cases From the Literature

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ABSTRACT. *Objective.* **Infantile Pompe's disease is a lethal cardiac and muscular disorder. Current developments toward enzyme replacement therapy are promising. The aim of our study is to delineate the natural course of the disease to verify endpoints of clinical studies.**

Methods. **A total of 20 infantile patients diagnosed by the collaborative Dutch centers and 133 cases reported in literature were included in the study. Information on clinical history, physical examination, and diagnostic parameters was collected.**

Results. **The course of Pompe's disease is essentially the same in the Dutch and the general patient population. Symptoms start at a median age of 1.6 months in both groups. The median age of death is 7.7 and 6 months, respectively. Five percent of the Dutch patients and 8% of all reported patients survive beyond 1 year of age. Only 2 patients from literature became older than 18 months. A progressive cardiac hypertrophy is characteristic for infantile Pompe's disease. The diastolic thickness of the left ventricular posterior wall and cardiac weight at autopsy increase significantly with age. Motor development is severely delayed and major developmental milestones are generally not achieved. For the Dutch patient group, growth deviates significantly from normal despite start of nasogastric tube feeding. Levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, or creatine kinase-myocardial band isoenzyme are typically elevated, although aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase increase significantly with age. The patients have fully deleterious mutations. Acid α-glucosidase activity is severely deficient.**

Conclusions. **Survival, decrease of the diastolic thickness of the left ventricular posterior wall, and achievement of major motor milestones are valid endpoints for therapeutic studies of infantile Pompe's disease. Mutation analysis and measurement of the α-glucosidase activity should be part of the enrollment program.** *Pediatrics* **2003;112:332–340;** ***Pompe's disease, α-glucosidase, acid maltase, enzyme replacement, glycogen storage disease type II.***

ABBREVIATIONS. ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; CK-MB, creatine kinase-myocardial band isoenzyme; $LVPW_d$, left ventricular posterior wall was measured at the diastole; CRIM, cross-reactive immunologic material; EKG, electrocardiogram; MRI, magnetic resonance imaging.

Pompe's disease, or glycogen storage disease type II, is a lysosomal storage disorder in which deficiency of acid α-glucosidase leads to accumulation of glycogen and finally to destruction of muscle tissue. Complete deficiency of α-glucosidase causes a progressive lethal cardiac and skeletal muscle disorder known as infantile Pompe's disease.[1] Partial deficiency leads to a milder late onset phenotype. The latter condition may present at any age and is subdivided in nonclassical infantile, childhood, juvenile, and adult Pompe's disease.[2–4] The estimated combined incidence is 1:40.000 births.[5,6] There is as yet no registered therapy for Pompe's disease, but the first clinical studies on enzyme replacement therapy with recombinant human α-glucosidase from rabbit milk and Chinese hamster ovary cells have started. The preliminary data of phase II studies in infantile patients are promising.[7–9] However, to fully appreciate the effect of enzyme therapy, precise knowledge is needed on the natural course of infantile Pompe's disease. This information is currently lacking.

Only 2 reviews on infantile Pompe's disease were published over the last 50 years. One review dates from 1950 and describes 14 patients.[10] The other review is from 1962 and describes 40 additional cases.[11] Notably, these reviews date from the time that the primary enzyme defect was still unknown.[12]

This review depicts the natural course of classic infantile Pompe's disease based on original data from 20 patients who where seen by the Dutch collaborative centers between 1980 and 1998 and a collection of 133 cases from the literature.

METHODS

We analyzed the clinical and laboratory data of the patients who were biochemically or genetically diagnosed with infantile

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Pompe's disease at the department of Clinical Genetics of the Erasmus University Rotterdam between 1980 and 1998. These data were compared with those obtained from the literature. We included all publications identified via Pubmed by a search for "infantile Pompe's disease," "infantile acid maltase deficiency," "infantile glycogenosis type 2," "infantile α-glucosidase deficiency," and "glycogenosis type 2a", written in English, German, French, Dutch, or Italian. Case reports cited in the collected articles and additional ones cited by Hirschhorn and Reuser[1] were added. We excluded publications lacking clinical information and cases of normal α-glucosidase activity (Danon's disease), prenatal death, and experimental treatment.

Information on clinical history, physical examination, and diagnostic data were collected. Data were often incomplete. Symptoms or findings of physical examination that were not reported were scored as negative.

Biochemical-Genetic Studies

Fibroblasts were homogenized in water, and 2000 × g supernatants were used to determine α-glucosidase activity.[13,14] Mutation analysis was performed using genomic and cDNA, as described earlier.[15] The functional effect of mutations was studied by assay of α-glucosidase synthesis and activity in transiently transfected SV_{40} transformed monkey kidney cells or in cultured fibroblasts of patients.[15,16]

Growth

Data on growth were collected and expressed in the standard deviation score for weight ([weight of the patient − weight according to the P50 for height]/standard deviation).

Clinical Chemistry

Aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and creatine kinase (CK) were measured according to the guidelines of the International Federation of Clinical Chemistry. Lactate dehydrogenase (LDH) was measured according to the guidelines of the Dutch Association of Clinical Chemistry. Creatine kinase-myocardial band isoenzyme (CK-MB) was measured by immune inhibition. All measurements were performed at an assay-temperature of 37°C.

Cardiology

The thickness of the left ventricular posterior wall was measured at the diastole ($LVPW_d$) by M-mode echocardiography in compliance with the guidelines of the American Society of echocardiography.[17]

Statistics

Characteristics for which repeated measurements within patients were available (weight, length, enzyme activities, $LVPW_d$) were analyzed using mixed model analysis of variance (random coefficients model for SAS PROC MIXED). Correlation coefficients given are Spearman r_s. Data given are medians, or indicated otherwise. Two-sided P values ≤ .05 were considered significant.

RESULTS

Population

Twenty infantile Pompe patients were diagnosed between 1980 and 1998; 14 patients were from Dutch, 4 from Turkish, 1 from Italian, and 1 from Taiwanese ancestry. The patients were admitted to 5 academic hospitals (Beatrix Clinic Groningen, Wilhelmina Children's Hospital Utrecht, University Medical Center Nijmegen, Emma Children's Hospital Amsterdam and the Sophia Children's Hospital Rotterdam). Thirty percent of the patients was female, 70% male. In literature we located 83 publications describing 133 patients, 42% female, 50% male.[2,10,11,18–97] Sex was not reported in 8% of the cases.

Molecular Characterization

All patients identified via the Department of Clinical Genetics Rotterdam had a severe α-glucosidase deficiency (Table 1). The median activity in fibroblast was 0.52 nmol MU/hour/mg protein (range: 0.18–1.15 nmol/hour/mg protein, normal value 36–166 nmol MU/hour/mg protein, median 84 nmol MU/hour/mg, $n = 254$). In 15 patients, we identified the mutations in both α-glucosidase alleles. In 2 more patients, 1 mutation was detected (Table 1). In total, 9 different mutations were found. The effect of 7 mutations was known: delT525,[98] del exon18,[23] Asp645His,[58,99] insC2741/insG2743,[15] Pro768Arg,[15] del Lys903,[100] and Gly309Arg.[101] All these mutations are fully deleterious and result in severe deficiency of α-glucosidase activity. Two new mutations were

TABLE 1. α-Glucosidase Activity, Mutations in the Lysosomal α-Glucosidase Gene, and the Resulting Amino Acid Changes per Patient

Patient	α-Glucosidase Activity	Nucleotide Change	AA Alteration	CRIM	Nucleotide Change	AA Alteration	CRIM*
1	1.15	DelT525[110]	Thr175→shift	−	Unknown		
2	0.59	DelT525[110]	Thr175→shift	−	Unknown		
3	0.43	DelT525[110]	Thr175→shift	−	DelT525[110]	Thr175→shift	−
4	0.29/0.42	DelT525[110]	Thr175→shift	−	DelT525[110]	Thr175→shift	−
5	0.38	DelT525[110]	Thr175→shift	−	InsA1827	Tyr609Ter	−
6	0.33	DelT525[110]	Thr175→shift	−	Del exon18[111]	Del 55aa 828→	+
7	1	DelT525[110]	Thr175→shift	−	Del exon18[111]	Del 55aa 828→	+
8	Undetectable	DelT525[110]	Thr175→shift	−	Del exon18[111]	Del 55aa 828→	+
9	0.18	Del exon18[111]	Del 55aa 828→	+	Del exon18[111]	Del 55aa 828→	+
10	Not available	Del exon18[111]	Del 55aa 828→	+	Del exon18[111]	Del 55aa 828→	+
11	0.44	Del exon18[111]	Del 55aa 828→	+	2639C→A	Ala880Asp	+
12	Undetectable	Del exon18[111]	Del 55aa 828→	+	3 nucleotide deletion	Del Lys903[100]	+
13	0.6	Del exon18[111]	Del 55aa 828→	+	925G→A[101]	Gly309Arg	+
14	0.73	1933G→C[58]	Asp645His	+	1933G→C[58]	Asp645His	+
15	0.7	2741AG→CAGG[15]	Frameshift	−	2741AG→CAGG[15]	Frameshift	−
16	1.1	2741AG→CAGG[15]	Frameshift	−	2741AG→CAGG[15]	Frameshift	−
17	0.52	2303C→G[15]	Pro768Arg	+	2303C→G[15]	Pro768Arg	+
18	1.1	Unknown			Unknown		
19	0.2	Unknown			Unknown		
20	0.23	Unknown			Unknown		

* Presence (CRIM+) or absence (CRIM−) of immunologically detectable α-glucosidase.

detected: Ala880Asp and InsA1827, resulting in Tyr609Ter. The latter mutation will certainly lead to loss of function. The effect of Ala880Asp was studied in transiently transfected SV_{40} transformed monkey kidney cells, and also leads to complete loss of α-glucosidase activity. The delT525 and del exon18 mutations were found most frequently, 10 times each. In all but 1 case the patient was from Dutch ancestry. One patient from Italy was homozygous for the exon18 deletion. Her parents came from the Italian region of Catania where this mutation prevails as in the Dutch population.[102] Of all mutations found in the Dutch patient group, the delT525 mutation, the insC2741/insG2743 mutation, and the Tyr609Ter mutation result in absence of cross reactive immunologic material ([CRIM]-negative). The delT525 mutation leads to frame shift and formation of unstable messenger. Two patients are homozygous for this mutation, and therefore completely CRIM-negative. Two of the 4 patients from Turkish ancestry are homozygous for the insC2741/insG2743 mutation and therefore also CRIM-negative. Both these patients were offspring of a consanguineous marriage. Another Turkish patient was homozygous for the Pro768Arg mutation, whereas in the fourth Turkish patient the mutation is as yet unknown. One patient from Taiwan appeared homozygous for the G1933C mutation known to occur in infantile patients from Taiwan and certain areas of China.[58,99] The great majority of case reports from literature is incomplete as to investigating the patients genotype. Related literature data are therefore not included in this review.

Course of Disease

First symptoms were noted at a median age of 1.6 months in both the Dutch patient group and in literature [2,10,11,18,20,21,23,25,27–38,40–46,48–60,62,63,65–76,78–88,91–96,99] (Table 2). Patients were hospitalized at median ages of 2.8 months in the Dutch patient group and 4.0 months in literature,[10,11,18–21,24,26,27,29,30,33,34,36–38,40–46,48,51–53,55,61–63,65,68,70,72,74,78,80,82,84,87,89,90,92,95–97,103] and diagnosed at respective ages of 5.3 and 4.5 months.[2,11,18,22,25,27,28,32,41,44,46,47,58,61,66,73,80,83,85,91,93,99] The median time from diagnosis to death was 2 months in both groups.[2,11,18,22,25,27,28,32,41,44,46,61,73,80,83,85,91,93] In the Dutch patient group, death occurred at a median age of 7.7 months. Patients described in literature died at a median age of 6.0 months.[2,10,11,18–21,23–34,36–44,46,48–57,59–65,67–75,78–97] The survival curve of both groups is presented in Fig 1. Only 1 Dutch infant survived beyond 1 year of age. This infant was born prematurely at a gestational age of 32 weeks. The age corrected for the duration of gestation was 10.6 months. The patients described in literature died in majority within the first year of life (109 of 119 patients). Ten patients survived beyond 1 year of age.[2,19,29,38,56,61,85,91,97] Only 2 patients were reported with ages of death above 1.5 year (29 and 34.5 months).[38,97]

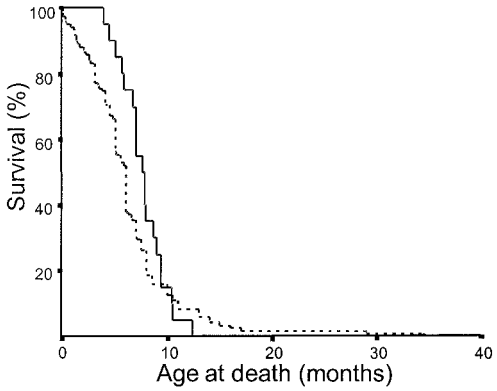

Fig 1. Survival curve of patients with infantile Pompe's disease. The Dutch patient population (solid line) and the literature cases (dashed line) are illustrated separately.

In the Dutch patient group, the clinical course of the CRIM-negative patients did not differ from the CRIM-positive patients. The 5 CRIM-negative patients died between 6.6 and 8.6 months of age.

Clinical History: First Symptoms

We kept record of the first symptoms of all Dutch patients. Information on an additional 66 cases was available from the literature.[2,10,11,18–20,22–24,26–32,34–38,41,42,44,45,48–52,55–58,60–76,78,79,81,82,84,85,87,88,92,95–97,99,104–106] Feeding problems and/or failure to thrive were the first symptoms in 55% of the Dutch patients and in 44% of the cases reported in literature. Motor problems, like muscular weakness, motor retardation, and paucity of movements, were the first symptom in 40% of the Dutch patient group and in 20% of the cases described in literature. Respiratory problems (like airway infections and respiratory difficulty) were the first symptom in 40 and 27% of the cases. Cardiac problems (like cardiac failure and rhythm disturbances) were noticed as first symptom in 15% of the Dutch patients and in 23% of the cases from literature (the total percentage exceeds 100% because patients may present with combinations of first symptoms).

Other less frequently reported symptoms were

TABLE 2. Course of Disease of the Dutch Population and of the Cases Collected From Literature

	The Netherlands				Literature			
	Median*	Mean*	Range*	*N*	Median*	Mean*	Range*	*N*
				20				133
First symptoms	1.6	1.9	0–6.8	20	1.6	2.1	0–11	107
Hospitalization	2.8	3.4	0–7.3	20	4.0	4	0–14	77
Diagnosis	5.3	4.8	0.6–9.3	20	4.5	5.4	0–23	22
Death	7.7	7.6	3.8–12.4	20	6.0	6.3	0–34.5	119
Time from diagnosis to death	2.0	2.8	0.1–6.4	20	2.0	2.7	0–10	18

* The age of the patients is given in months.

discomfort (like malaise, sweatiness, fatigue, irritability, and a weak cry) and gastrointestinal complaints (like constipation, vomiting, and regurgitation). Neurologic symptoms like spasm and tremor were noticed in 2 Dutch cases. In 3 cases from literature, mental retardation was suspected.[27,38,75] Reasons for hospitalization were respiratory problems, cardiac problems, feeding problems, and growth retardation in decreasing order.

Physical Examination

The 20 Dutch patients were physically examined. An additional 103 physical examination reports were available from literature.[2,10,11,18–23,26–42,44–46,48–52,55–57,59–65,67–74,76–79,81,82,84,85,87,88,92,95–97] At first sight, patients were tachy- or dyspnoeic (75% of the Dutch patients and 41% of the cases from literature), pale (40% of the Dutch patients, 20% of the cases described in literature), and/or cyanotic (30% and 23%, respectively). An enlarged tongue was noticed in 45% of the Dutch patients and 29% of the cases from literature. The Dutch patients typically were hypotonic (95%). Hypotonocity was reported to a lesser extent in literature (52%). In 75% of the Dutch patients and in 46% of the cases from literature, a heart murmur was present. A gallop rhythm was reported in 17% of the cases from the literature. Auscultation of the lungs was abnormal in 55% of the Dutch patient group and in 47% of the cases reported in literature. At palpation of the abdomen a moderate hepatomegaly was found in 90% of the Dutch patients and reported in 29% of the cases from literature (median size 3 and 3.2 cm below the costal margin, respectively). A moderate splenomegaly was found in 15 and 6% of the patients, respectively (median size 2 cm below the costal margin in both populations). Absent deep tendon reflexes (35% of the Dutch patients, 33% of the cases from literature) was the main abnormality observed during neurologic examination. Incidentally, tongue fibrillations (3%), absence of tongue movements (2%), and spasms of the legs (2%) were reported in literature. In the Dutch patient group these were not noticed.

Motor Development

A complete set of data on motor development was available for 16 Dutch patients. None of these patients ever learned to turn, sit, or stand. Of the 133 patients reported in literature, only 2 patients were reported to turn from supine to prone position.[18,63] The age at which they achieved this motor milestone was not mentioned, but they lost this ability at the age of 4 and 7 months, respectively. Three patients were reported to sit. One achieved this motor milestone at the age of 6 months and subsequently lost it at the age of 7 months.[63] The other patients were reported "no longer to sit without support" and "no longer to support themselves in a sitting position" at ages of 7.5 months[72] and 10.5 months,[33] respectively.

Growth

Longitudinal data on weight, length, and head circumference were available for 18 of the Dutch patients (mean duration of follow-up 4.3 months).

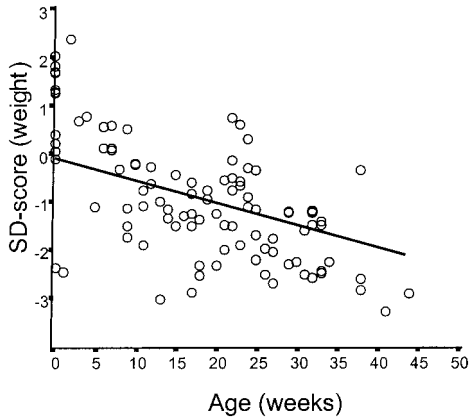

Fig 2. Standard deviation score of weight versus age in weeks ($P = .001$) for the Dutch patient population. Standard deviation score = [weight of the patient-weight according to the P50 for weight]/standard deviation of weight.

The standard deviation score for weight decreased significantly with age ($P = .001$, Fig 2), showing a deviation from the normal weight curve, despite the start of nasogastric tube feeding in 14 patients. Increase of length and head circumference with age was normal.

Clinical Chemistry

Levels of CK, CK-MB, LDH, ASAT, and ALAT generally appeared to be increased in the Dutch patients ($n = 19$). The median value of CK was 690 IU (range: 175-2307 IU, upper limit of normal 295 IU (P_{95}), number of measurements 40). A normal CK value was measured 5 times. The median value of CK-MB was 29 (range: 14–64 IU, upper limit of normal 18 IU, number of measurements 20). CK-MB was normal in 3 measurements. The median value of LDH was 1956 IU (range: 801-5714 IU, upper limit of normal 1097 IU, number of measurements 35). LDH was normal in 4 measurements. The median value of ASAT was 321 IU (range: 115–859 IU, upper limit of normal 89 IU, number of measurements 51) and of ALAT 184 (range: 9–397 IU, upper limit of normal 60 IU). ASAT and ALAT were one time normal in one patient, but elevated in later measurements. In none of the cases normal values for CK, CK-MB, LDH, ASAT, and ALAT were found at the same time. There was a significant increase of LDH, ALAT, and ASAT with age ($P < .001$, Fig 3). Data from literature were too scarce to draw conclusions. Control ranges and assay temperatures were often lacking.

Cardiology

All available chest radiographs of the Dutch patients ($n = 19$) showed a cardiomegaly at ages ranging from 0 to 7.2 months. In literature an increased heart size was reported in 99% of the cases described ($n = 82$).[10,11,18–21,26–42,44,45,48–52,55,56,60,61,63–68,70–72,74,76–79,81–83,85,87,88,95,97,107]

On the electrocardiograms (EKGs), a left ventricular hypertrophy was noticed in all Dutch patients ($n = 19$). A biventricular hypertrophy was seen in 84%, and an atrium hypertrophy in 11% of the patients. In literature, left ventricular hypertrophy was

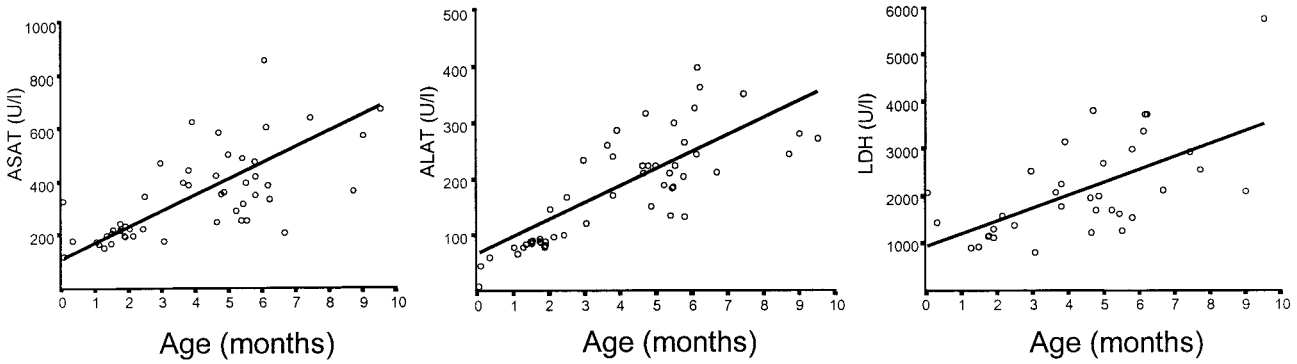

Fig 3. Increase of ASAT, ALAT, and LDH with age for the Dutch patient population ($P < .001$ for ASAT and ALAT, and $P = .004$ for LDH).

reported in 60 (83%) of 72 cases.[2,10,11,18,19,22,24,26,27,29,30,32,34–41,44,45,49,50,52,55,56,60,61,63–68,70,72,76–79,81,83,85,87,88,95,97] In 10 cases, the cardiomegaly was noticed on the chest radiograph, but not on the EKG. In only 2 patients, the EKG was totally normal.[2,88] Atrium hypertrophy was seen in 4% of the cases described in literature.

Another EKG abnormality reported is a borderline to shortened PQ-interval. This was present in 58% of the Dutch patient group (median 0.08 seconds) and in 51% of the cases described in literature (median 0.08 seconds). Repolarization disturbances like T-inversion and ST-depression were present in 84% of the Dutch and 56% of the literature cases.

Echocardiographic data of 18 Dutch patients were available (Fig 4A). All patients had a cardiac hypertrophy at ages varying from 0.1 to 8.8 months, as shown by the increased thickness of the left ventricular posterior wall and the intra-ventricular septum. The thickness of the left ventricular posterior wall increased significantly with age ($P = .01$, Fig 4A). In literature, the echocardiographic data of 23 patients were presented.[18,19,26,28,32,35,37,39,49,56,60,66,67,76,77,81,83,108] All patients had a cardiac hypertrophy, as illustrated by the thickening of the left ventricular posterior wall and/or intra-ventricular septum.

In 67 cases, heart-weight at obduction was reported.[10,11,18–21,24,26,27,29,30,33,34,36–38,40,41,44–46,48,51–53,55,61–65,68,70,72,74,78,80,82,84,87,89,92,95–97] The heart weight shows a significant increase with age ($r_s = 0.57$, Fig 4B) in accordance with the cardiac ultrasound data of the Dutch patients. Outflow tract obstruction was described in 8 cases from literature,[11,32,39,45,49,76,83,109] as observed either by echocardiography, catheterization, or autopsy (6%).

When all cardiac data from the literature are compiled there is information available for 109 patients; 107 of them have a cardiomegaly and 2 do not.[2,88]

Neurologic Diagnostics

Data on brain imaging were available for 8 of the 20 Dutch patients. An ultrasound of the brain was performed in 6 patients, a magnetic resonance imaging (MRI) in 2, and a computed tomography in 2 patients. The ultrasound was normal in all 6 patients. A MRI performed in 1 of these patients was also normal. Computed tomography made in 2 additional patients showed some widening of the anterior horn of the left ventricle in one patient and a possible widening of the peripheral liquor spaces in the other patient. The MRI in the latter patient revealed central and cortical atrophy.

DISCUSSION

With the phase II clinical studies on the effect of enzyme replacement therapy in Pompe's Disease underway, it becomes increasingly important to achieve accurate knowledge on the natural course of the disease to verify endpoints. The first results of enzyme replacement therapy in infants are promising. Patients seem to survive longer and an effect on cardiac hypertrophy is observed. However, systematic surveys of larger groups of untreated patients, needed to fully appreciate the effect, are lacking.

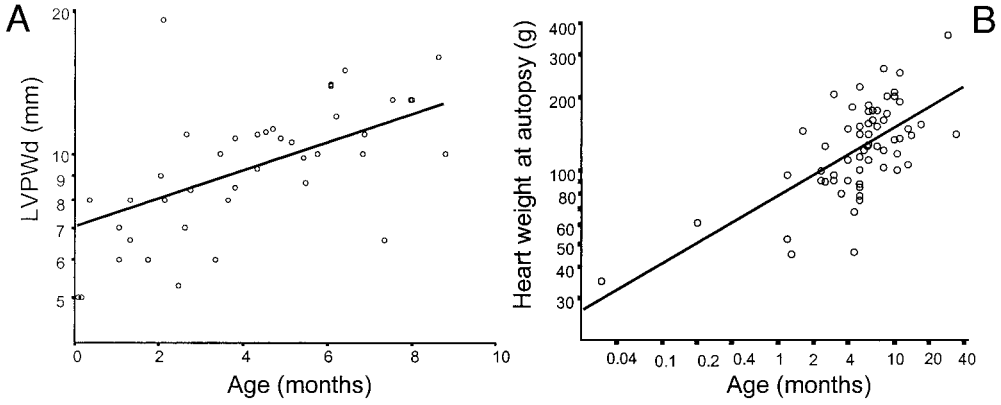

Fig 4. A, Increase of the $LVPW_d$ with age ($P = .01$). B, Increase of heart weight with age ($r_s = 0.57$).

Therefore, we followed the natural course of infantile Pompe's disease in 20 Dutch patients and studied the published case reports of an additional 133 patients. The Dutch patients were identified via the enzyme diagnostic laboratory of the Department of Clinical Genetics, Erasmus University, Rotterdam, thereby precluding selection based on preset clinical criteria.

The literature data show that Pompe's disease occurs worldwide. The course of the disease is essentially the same in the Dutch and the general patient population. Symptoms start in both groups shortly after birth (median age: 1.6 months). Age at hospitalization (2.8 and 4.0 months), diagnosis (5.3 and 4.5 months), and death (7.7 and 6.0 months) also compare well.

All Dutch patients have a severe α-glucosidase deficiency of <1.5% of the median control value (median 0.6% of control value) in fibroblasts. Patients from Taiwanese, Turkish, Dutch, and Italian ancestry are included. Mutations were discovered in 32 of 40 mutant alleles. All revealed fully deleterious mutations. The frequently occurring IVS1 (−13T→G) mutation, typically associated with late-onset Pompe's disease was not present in the infantile patient group. This finding is consistent with the prediction that only the combination of 2 fully deleterious mutations leads to the classical early-onset phenotype. Patients from different ethnic origin had different mutations. For instance, delT525 and del exon18 are common among the Dutch patients. We detected 2 new severe mutations: Ala880Asp and InsA1827 (leading to Tyr609Ter). Their effect was demonstrated by expression studies. Currently, >80 fully deleterious mutations are known (www.pompecenter.nl).

In both patient groups feeding problems, failure to gain weight, muscular weakness, motor retardation, cardiac problems, respiratory difficulty, and airway infections were frequently reported as first symptom of the disease. Once referred to the hospital, symptoms of respiratory and/or cardiac failure were evident. The children mostly were tachy- and/or dyspnoeic and often pale or cyanotic. On clinical examination, a cardiac murmur was frequently present. The moderate enlargement of the liver is assumed to result from glycogen storage, but may also result from cardiac decompensation. Hypotonicity was noted as a prominent feature in the Dutch patients, but is less reported in the literature. We consider it unlikely that the Dutch and general patient group differ in this aspect and attribute the apparent difference to incompleteness of the case reports. Absence of deep tendon reflexes was the most common abnormality on neurologic examination. Enlargement of the tongue was reported in less than half of the patients (45% of the Dutch cases and 29% of the cases from literature).

The following findings are key elements for the definition of the classical infantile subtype of Pompe disease. First, infantile Pompe patients typically die in the first year of life. Death occurs at a median age of 7.7 months in the Dutch patient group and 6.0 months in literature. Similar survival data were reported by Amalfitano et al[7–9] (mean age of death 8.6 months) and Slonim et al[2–4] (calculated median age of death 8.0 months). There is no significant difference between the age of death of CRIM-negative and CRIM-positive patients in the Dutch patient group. A minority of patients became older than 1 year (8%). Ninety-eight percent of all patients died before the age of 1.5 years. None of the patients grew older than 2.9 years. Based on $n = 139$, statistical calculation shows that the upper limit of 95% confidence interval for 3 years survival equals 3%.

Second, infants with classical Pompe's disease have a rapidly progressive cardiac hypertrophy. The diastolic thickness of the left ventricular posterior wall appears to be a good measure for follow-up. The left ventricular mass or left ventricular mass index might be used as follow-up on cardiac weight. In the Dutch patients, a cardiomegaly was found at any time point in life, even when the chest radiograph, the electrocardiogram, or echocardiography was performed at birth. This indicates that cardiac hypertrophy already develops during gestation. In literature, 107 of the 109 patients appeared to have a cardiomegaly during cardiac evaluation. From the 2 patients from literature who were reported to have a normal heart on EKG and chest radiograph, 1 had an unusual high level of residual α-glucosidase activity (36% of normal in fibroblasts, and 46% of normal in muscle), which does not combine with infantile Pompe's disease.[88] The other patient had 2 brothers who died at relatively advanced age (3 and 4 years of age) as compared with all other cases in this study.[2] From the combined data we conclude that the absence of cardiomegaly is atypical for classical[2–4] infantile Pompe's disease.

Three other key elements of infantile Pompe's disease are motor development, growth, and laboratory findings. Motor development is severely delayed. Important milestones are generally not achieved or lost shortly after acquisition. None of the Dutch patients ever learned to turn, sit, or stand. In literature, only 3 of the 133 patients were reported to turn or sit, but subsequently lost this ability quickly.

Weight gain appears to be significantly reduced in infantile patients, despite the start of nasogastric tube feeding.

The levels of ASAT, ALAT, LDH, CK, and CK-MB are typically elevated in infantile Pompe's disease. None of the Dutch patients has normal values for ASAT, ALAT, LDH, CK, and CK-MB at the same time. ASAT, ALAT, and LDH increase significantly with age and appear an even better marker of disease progression than CK. It is most likely that the enzymes originate from muscle. However, it is not excluded that the liver contributes in part.

Based on the data obtained in our study on the natural course of infantile Pompe's disease, it is concluded that survival is a good endpoint for enzyme replacement therapy studies. In an ongoing open label enzyme replacement therapy study, we currently treat 4 infantile Pompe patients with recombinant human α-glucosidase from rabbit milk.[7–9] All 4 patients are still alive at the age of 3 years. Based on this result, statistical calculations show that the 95% confidence interval for the 3 years survival percent-

age ranges from 40 up to 100% in a group of infantile patients receiving enzyme therapy. This means that if the enzyme therapy study with the same therapeutic regimen would be repeated with a larger number of infants, the 3-year survival percentage is expected to be 40% at least. Comparing this figure with the upper limit of the 95% confidence interval for 3 years survival of untreated children (this manuscript), which is 3%, there is a strong indication that enzyme therapy has an effect on survival.

However, because optimization of care (like application of artificial ventilation, treatment of infections, and other supportive measures) also may prolong survival of untreated children, the results obtained with enzyme therapy should ideally be compared with results obtained in a matched group of children, who receive exactly the same supportive care but no enzyme therapy.

Based on the assumption that 1-year survival increases from 10% in the "placebo" group to at least 75% in the enzyme replacement therapy group, it is calculated that in a placebo-controlled enzyme therapy study 11 patients have to be included in both the treatment and the placebo group to obtain 80% power at $\alpha = 0.05$ (Fisher exact test) for the comparison of survival.

A decrease of cardiac hypertrophy, evidenced by a decrease in the diastolic thickness of the left ventricular posterior wall or left ventricular mass index can provide additional proof for efficacy of therapy and serve as secondary endpoint. Improvement of clinical condition should accompany the latter finding to demonstrate the clinical benefit for the patients. Achievement of major milestones provides evidence for the efficacy of enzyme therapy on motor function.

If for ethical reasons a non-placebo-controlled study is performed and historical data are used as control, it is of utmost importance that no selection bias is introduced. In our opinion, molecular genetic delineation of the patients should always be part of the enrollment program, besides characteristic clinical and cardiac features, to identify patients with noninfantile phenotypes, who have a prolonged natural course.

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BLAME TECHNOLOGY FOR OBESITY

"Technology may be fattening. Something surely is. In the past quarter-century, American waistlines have bulged, and obesity has become epidemic. The government's authoritative National Health Examination Survey found 30% of adults in 1999–2000 were obese by the technical medical definition. That's up from 23% in 1988–1994 and 15% in 1976–1980. . . Some blame the food industry for deceiving us into eating more fatty and caloric foods. Others link the increase in weight to the decrease in smoking. Still others blame a sedentary lifestyle in which playing games on computer screens replaces athletic activity, and cars and elevators eliminate the need to walk. It's obvious that technology has made us richer and food cheaper, in terms of the hours we have to work to feed ourselves. And technology has changed the physical nature of daily work."

Wessel D. *Wall Street Journal*. February 13, 2002

Noted by JFL, MD

The Natural Course of Infantile Pompe's Disease: 20 Original Cases Compared With 133 Cases From the Literature

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