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ORIGINAL ARTICLE

Fractures in children with Pompe disease: a potential long-term complication

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Abstract
Background Pompe disease (glycogen storage disease type II or acid maltase deficiency) is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase (GAA). Classic infantile-onset disease, characterized by cardiomegaly and profound weakness, leads to death in the first year of life from cardiorespiratory failure. Reversal of cardiomyopathy and improved motor function have been shown in clinical trials of rhGAA enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme), recently approved for clinical use. Increased survival potentially unmasks long-term complications of this previously lethal disease, including risk of skeletal fracture, recently identified at our institution and not previously reported in children with Pompe disease.
Objective To report the risk of fracture in children with Pompe disease with increased survival with ERT.
Materials and methods We present four cases of fracture in patients with classic infantile Pompe disease treated with ERT at our institution, and review a study database for additional reports of fracture in this population.
Results We review 19 fractures in 14 children with Pompe disease on ERT.
Conclusion Radiologists should be familiar with and vigilant for the association of fractures and increased survival on ERT in children with Pompe disease. We discuss potential mechanisms, implications for radiographic surveillance, potential intervention, and needs for further research.

Keywords Pompe disease · Fracture · Bone density · Radiography · Weight bearing · Children

Laura E. Case and Rabi Hanna contributed equally to this study.

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Introduction

Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase (GAA). The estimated incidence of Pompe disease across the disease spectrum (infantile and late-onset)

is 1:40,000 births. Children might present with classic infantile, non-classic infantile/atypical, or juvenile-onset Pompe disease. Classic infantile-onset disease presents with cardiomegaly, hypotonia, macroglossia, failure to thrive, and hepatomegaly and is universally fatal from cardiorespiratory failure, usually within the first year of life. All types are characterized by significant progressive myopathy and respiratory involvement [1–5].

Clinical trials of enzyme replacement therapy (ERT) using rhGAA derived from Chinese hamster ovary (CHO) cells [6–12] have shown reversal of cardiomyopathy and improved motor function in infants and children with Pompe disease. Alglucosidase alfa (Myozyme), rhGAA manufactured and distributed by Genzyme Corporation for ERT and used in many of the clinical trials, has recently been approved for use as a treatment for Pompe disease in the US by the Food and Drug Administration (FDA), and in Europe by the European Medicines Agency (EMEA). Children are living longer, some achieving milestones that would not have otherwise been reached such as sitting, standing, walking and running [6, 9, 11]. Others with a less robust motor response remain unable to support weight through the lower extremities or (a very small subset) show a clinical decline.

Long-term complications of this previously lethal disease can emerge with increased survival. One of the long-term complications appears to be a risk of fractures, recently recognized at our institution and not previously reported in children with Pompe disease. In this investigation, we present four cases of fracture in patients with classic infantile Pompe disease treated with ERT at our institution and review a study database for additional reports of fracture in this population.

Materials and methods

Patient identification

Four boys with infantile-onset Pompe disease (out of 25 children with infantile-onset Pompe disease treated with ERT at our institution) with a mean age of 8.25 months (range 2–18 months) at the start of ERT developed fractures at a mean age of 16.5 months (range 13–21.5 months). All patients were receiving ERT at the time of fracture, and were enrolled in open-label clinical trials exploring the safety and efficacy of CHO cell-derived rhGAA ERT at Duke University Medical Center. All patients had nutrition evaluations by a metabolic dietitian with experience in Pompe disease, at baseline or within 8 weeks of starting ERT, with follow-up nutrition evaluations every 12 weeks or as clinically needed. Following Institutional Review Board approval and written informed consent, a systemic chart review of these patients with fractures was conducted.

After recognizing this complication, Genzyme Corporation informed other sites of this potential complication in patients with Pompe disease. A search of the Genzyme Pharmacovigilance safety database for fractures occurring from 2001 to 2006 in patients receiving ERT was conducted. MedWatch forms were produced and reviewed after identifying 15 cases of fracture in ten children with Pompe disease who were reported from other institutions. Two children had more than one fracture. Many patients who experienced fracture were also reported as having decreased bone density, referred to as "osteopenia" or "osteoporosis." At this time, because of insufficient epidemiological data to define osteopenia and osteoporosis in children, the term "low bone mineral density (BMD) for chronological age" has been recommended and is used in this paper for children with Z scores less than −2.0 on dual energy X-ray absorptiometry (DEXA) [13]. The term decreased bone density (BD) is used when decreased bone density, "osteopenia" or "osteoporosis" were subjectively identified by diagnostic imaging but not quantified by DEXA.

Imaging evaluation

All radiographic examinations for the four patients identified with fracture at our institution were reviewed by a single certified (CAQ) pediatric radiologist with 15 years of experience (D.F.). Examinations were reviewed and conclusions were confirmed as agreeing with the original dictated radiology reports.

Results

Case reports

A summary of the demographic and clinical information for the four patients identified with fracture at our institution is presented in Table 1.

Case 1

This full-term boy with infantile-onset Pompe disease started ERT at age 4 months. At baseline examination at 3½ months of age, he was profoundly hypotonic with minimal active movement. Over the next 3 months he showed motor improvement, even prop-sitting with minimal support, but by age 8 months a motor decline was noted, and he became ventilator-dependent at age 9 months, once again profoundly hypotonic with no antigravity movement. At age 16 months he was diagnosed with a fracture of the right femur with diffuse low BD, with no trauma reported. He was placed in a Pavlik harness for 3 weeks. The fracture healed well in

Table 1 Demographic and clinical information for the four patients with infantile-onset Pompe disease identified with fracture at our institution

Patient	Gender	Age (months)			Fracture		Diet	Motor skills before ERT	At time of fracture				
		Diagnosis	ERT start	Fracture	Location	Type			Motor skills	Growth parameters (percentiles)			Medication[a]
										Height	Weight	Head circumference	
1	M	2	4	16	R femur		N/G Enfamil	Head lag; frog legged; unable to bear weight when held standing	Frog legged; tube-fed; vent-dependent; non-weight bearing	50th	50th	5th	Cyclophosphamide, diphenhydramine
2	M	In utero	2	13	R femur, subcapital neck		PO Prosobee	Head lag; frog legged; able to bear weight intermittently when held standing	Frog legged; tube-fed; vent-dependent' non-weight bearing	25th	10th	50th	Glycopyrrolate, ranitidine, diphenhydramine
3	M	8	18	21.5	R femur	Oblique	N/G Pediasure	Head lag; frog legged; vent-dependent; unable to be supported in standing	Frog legged; tube-fed; ventilator-dependent; non-weight bearing	50th	50th	90th	Chlorothiazide
4	M	6	9	15.5 (fracture identified)	T8 vertebra	Compression	PO Enfamil	Head lag; not rolling over; unable to bear weight when held in standing	Good head control; sitting and rolling independently; history of sitting with rounded back; creeping on hands and knees with assistance; pulling to stand with knee support required to maintain standing; using stander at home	75th	10th	50th	Digoxin, captopril, furosemide

[a] Medication with potential impact on bone density.

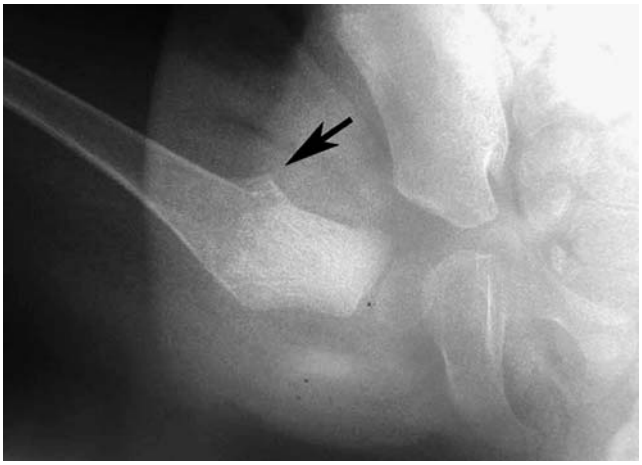

Fig. 1 A 13-old-month boy with Pompe disease treated with ERT now with a right femur fracture. Collimated frog-leg lateral view of the right femur shows the cortical disruption (*arrow*). Note also decreased bone density

6 weeks. Nutrition review showed adequate calcium and vitamin D intake and electrolytes and parathyroid hormone (PTH) were all normal. He never stood or walked, was never able to support weight through the lower extremities when held in standing, and had not used a standing device prior to his diagnosis of fracture.

Case 2

This full-term boy with infantile-onset Pompe disease started ERT at age 2 months and 3 weeks. He initially showed improvement in motor function on ERT, prop-sitting momentarily by himself and able to support weight through the lower extremities when held in standing at 5 months of age, but motor skills declined and he became ventilator-dependent at 8 months of age. At 13 months, he was again extremely hypotonic, with limited movement of the extremities. While changing his diaper at 13 months of age, his mother noted swelling and redness in the region of his right thigh. Radiographs revealed a subtrochanteric fracture of the right femur (Fig. 1). There was no known history of trauma. Low BD was also noted on his long bone films. He was placed in a Pavlik harness for 3 weeks. The fracture healed well in 6 weeks. Nutrition review showed adequate calcium and vitamin D intake, and electrolytes and PTH were all normal. He never stood or walked and never used a standing device but had been able to support weight through the lower extremities when held in standing at 5 months of age.

Case 3

This full-term boy was profoundly hypotonic when diagnosed with infantile-onset Pompe disease at age 8 months and when he started ERT at age 18 months. He showed slight improvement in movement of the hands and feet with ERT but remained extremely hypotonic with minimal antigravity movement. At the age of 21 months, while in the hospital for a gastrostomy tube replacement, tenderness and swelling of the right leg was noted and radiographs revealed an oblique fracture of the right femur with diffuse low BD (Fig. 2). There was no known history of trauma. He was treated with a modified Pavlik harness, and the fracture healed well. Metabolic skeletal survey showed diffuse low BD. Nutrition review showed adequate calcium and vitamin D intake, and electrolytes and PTH were normal. He never sat independently, stood or walked, was never able to support weight through the lower extremities when held in standing, and had not used a standing device prior to his diagnosis of fracture.

Case 4

This full-term boy with infantile-onset Pompe disease began ERT at age 9 months, at which time he was hypotonic and could not support weight through the lower extremities when held in standing. By 15½ months, he was able to sit independently, creep on hands and knees, pull to stand and stand with support, and used a standing device. Chest radiograph at age 15½ months for follow-up of cardiomegaly incidentally showed narrowed vertebral bodies and a compression fracture of T8 (Fig. 3). A metabolic survey showed diffuse decrease in BD (Fig. 3). There was no known history of trauma and no clinical manifestations of fracture. Nutrition review, electrolytes, calcium, vitamin D, alkaline phosphatase and PTH were all normal.

Review of reports of fractures in patients receiving ERT at other institutions

A summary of the demographic and clinical information for the ten children with Pompe disease on ERT at other institutions with fracture reported in MedWatch reports from 2001 to 2006 is presented in Table 2.

Patients with Pompe disease on ERT in different clinical trials from 2001 to 2006 were reviewed via MedWatch reports. A total of 15 fractures were noted in ten children, with a total of 11 femoral fractures, 2 tibial fractures, and 2 humeral fractures (Table 2). Of the two children who had multiple fractures, one had four fractures and the other had three fractures. The total population of individuals with Pompe disease receiving ERT in May 2006 was approximately 300.

The median age at which the first fracture occurred in the 14 children reported was 22.75 months (ranging from 13 months–8 years). The median age at which ERT was initiated was 8.5 months (ranging from 2 months–8 years). The median time on ERT prior to the first fracture was

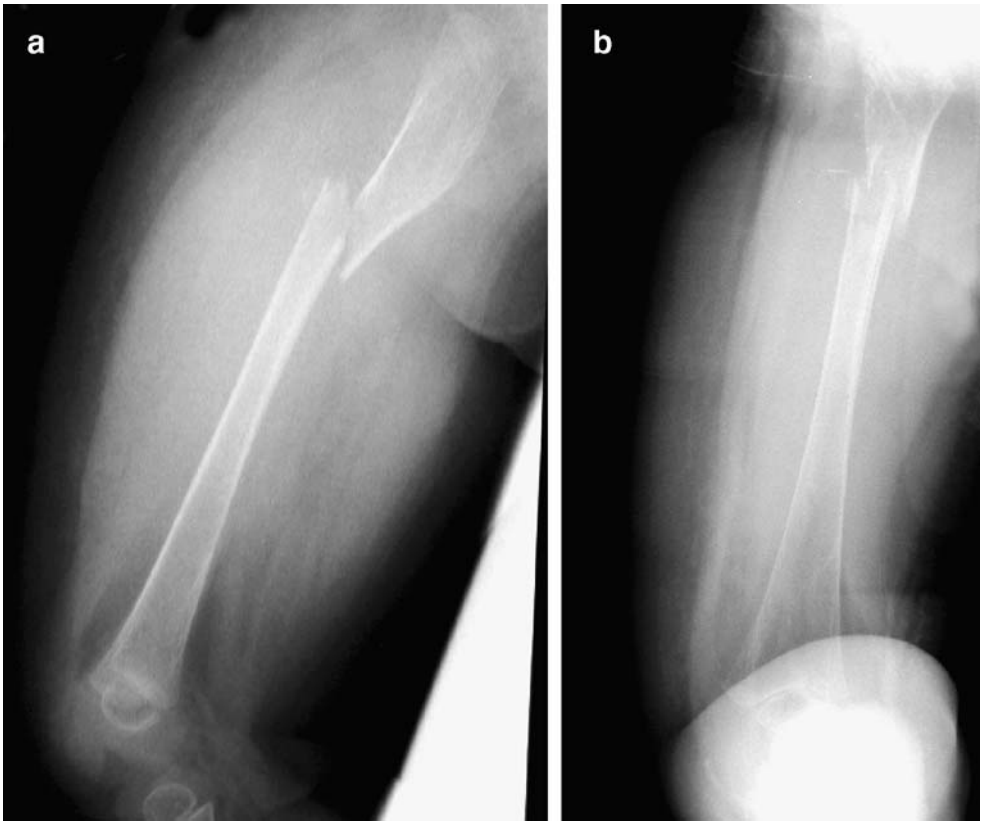

Fig. 2 A 21-month-old boy with Pompe disease treated with ERT with a femur fracture. Slightly oblique frontal view (**a**) and true lateral view (**b**) of the right femur demonstrate acute mildly angulated femur fracture. Mild decrease in bone density is also noted

12 months (ranging from 2–33 months). All children who sustained long-bone fractures showed a lack of weight bearing at the time of fracture. None of the children treated at our institution who were walking or who were weight bearing had long-bone fractures. Although the four children with fracture treated at our institution had no history of trauma, some of the fractures reported via MedWatch were associated with minimal or mild trauma of various types, with a few fractures occurring in physical therapy sessions.

Discussion

Pompe disease is both a neuromuscular disease and a lysosomal storage disease, and increased risk of fracture in infants and children with Pompe disease might be expected secondary to a decrease in bone strength from nutritional factors, decreased muscular activity, decreased weight bearing, and perhaps metabolic effects of the lysosomal storage disturbance. An increased incidence of fracture has been reported in other motor unit diseases [14–24] and in other lysosomal storage diseases [25, 26]. However, fractures were not described as a complication of Pompe disease in infants and children prior to the advent of ERT.

We report here on fractures in four of our patients with infantile-onset Pompe disease on ERT and 15 additional cases of fracture in ten patients on ERT that were reviewed with MedWatch reports provided by Genzyme Pharmacovigilance. A number of factors might contribute to the risk of fracture. Decreased BD was documented in 13 of the 14 patients reported here and is presumed to be a substantial risk factor for fracture, as it is in other neuromuscular disorders [15, 27–31]. Decreased BMD is probably multifactorial in infants and children with Pompe disease with weakness, immobility, decreased physical activity, and decreased weight bearing significant, as in any underlying myopathy [15, 21, 32, 33], possibly exacerbated by feeding difficulties, medication such as non calcium-sparing diuretics (calciuric diuretics) and steroids. Other causes might include factors such as stage of underlying disease, muscle fiber type, the presence or absence of cross-reacting immunological material (CRIM) [11], with CRIM-negative status a potentially negative prognostic factor [6, 11, 12], and other causes not currently recognized.

The evolution of BD in any given child is probably multifactorial as evidenced by the fact that BMD measured in children with Pompe disease on ERT does not necessarily correlate with gross motor status, level of weakness, and weight-bearing status [34], a lack of correlation that is also true in spinal muscular atrophy [32]. Decreased BD has been reported in other lysosomal storage diseases with more intrinsic bony mechanisms identified, including osteonecrosis and imbalance between osteoblast and osteoclast activity [25, 26], factors that have

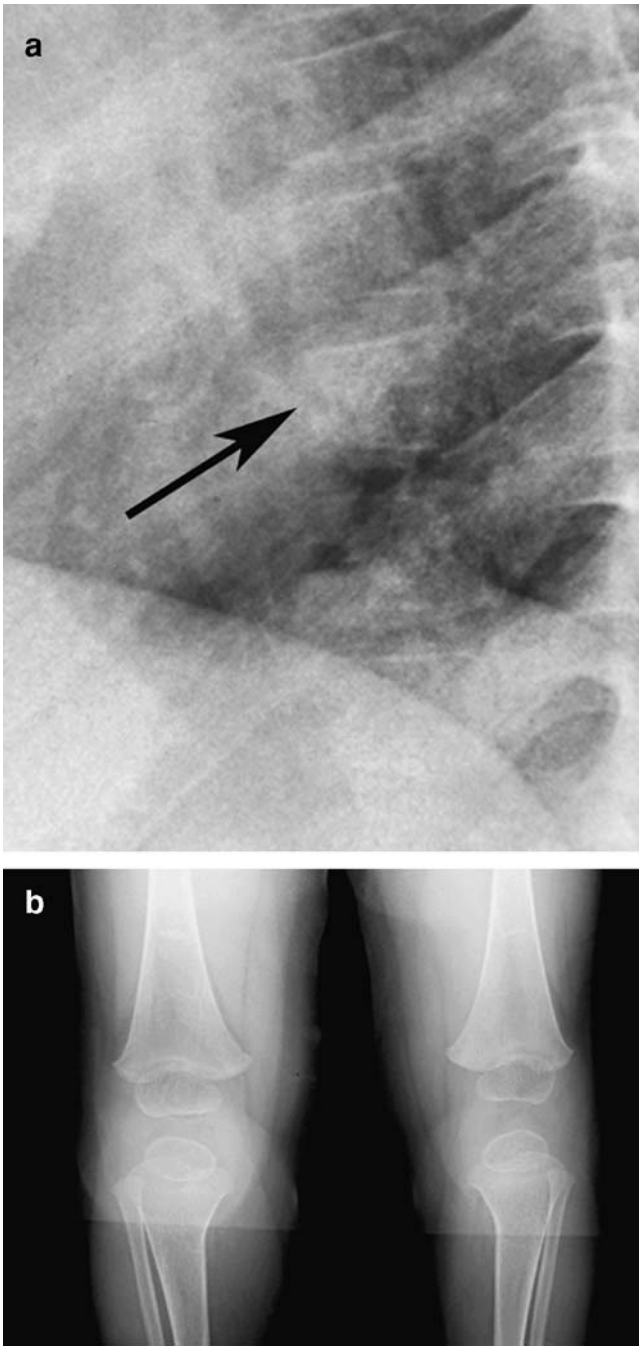

Fig. 3 A 15-month-old boy with Pompe disease treated with ERT now with decreased bone density and compression fracture. **a** Lateral, collimated view of the lower thoracic spine shows anterior wedge deformity (*arrow*) of the T8 vertebral body. **b** AP view of both knees demonstrates decreased bone density

not yet been studied in Pompe disease. Not all patients with Pompe disease and decreased BD experience fractures [34]. Strength and integrity of bone depends not only on BD but on complex characteristics of the bone including the proportion and arrangement of cortical and trabecular bone, patterns of trabecular systems, and the configuration and alignment of bone, all of which depend in part on normal muscle pull and normal weight bearing. These characteristics are not reflected by DEXA scores because DEXA does not distinguish between trabecular and cortical bone [15], which could be why a relationship between the risk of fracture and decreased BMD as measured by DEXA and based on Z scores in children has not been established [15]. Another factor that could predispose to fracture is muscle deficiency. Factors such as the ability of muscle to provide stability, protection and shock absorption during force application are compromised in the presence of weakness and could contribute to the risk of fracture.

The youngest age at which fracture occurred in the children reported in this series was 13 months, which is beyond the previously typical age of survival of most children with infantile-onset Pompe disease without ERT, and it is possible that children did not survive long enough in the past for fractures to occur and be observed and reported. To date, there has been only a single case of fracture reported in the literature, in an adult [35] with late-onset Pompe disease. He was not on ERT and developed a thoracic vertebral compression fracture (T12).

In our case series of four children with infantile-onset Pompe disease, magnesium, calcium, phosphorus and serum PTH levels, where available, were normal. All patients had an adequate calcium and vitamin D intake and overall were in a good state of nutrition as verified by our metabolic dietician. All patients also had decreased BD as seen on radiographic evaluation. Laboratory work-up was essentially normal and excluded vitamin D or hyperparathyroidism as a cause for their decreased BD.

Biomechanical compromise from weakness and lack of normal weight bearing might have had a significant role in fracture risk in these patients. In all three cases of femur fracture in our patients, the children were profoundly hypotonic, with lower extremities essentially immobile in flexion/abduction/external rotation, and were unable to support weight through the lower extremities when held in standing at the time of fracture. The ten additional children on ERT identified and examined with MedWatch with 15 long-bone fractures had significant residual motor impairment and were not weight bearing at the time of fracture. Patient 4 had a thoracic fracture but did not have a long-bone fracture. He had a history of sitting with an extremely rounded back, secondary to decreased strength in spinal extensors and decreased hamstring extensibility. Spinal kyphosis is a position associated with vertebral fractures [36] and a position in which loading through the vertebral bodies would be decreased or altered [37].

This study is the first to show that insufficiency fracture can be a complication in children with Pompe disease who are now surviving longer with ERT and that the fracture could be related, at least in part, to a combination of residual weakness, decreased BD, and lack of weight bearing each of

Table 2 Demographic and clinical information for the ten patients with Pompe disease identified with fracture in MedWatch reports

Patient	Gender	Age (months)		Fracture	Gross motor	Decreased bone density	Medication at time of fracture[a]
		ERT start	Fracture				
5	F	9	32	L femur	Immobile	Yes	Hydrochlorothiazide, spironolactone, vitamin D, calcium, furosemide
6	F	33	48	L femur	Immobile	Yes	Vitamin D
7	M	36	48	L femur	Wheelchair; no weight bearing	Unknown	Hydrochlorothiazide, furosemide, spironolactone, propranolol
8	F	8	15	L femur	Immobile	Yes	Unknown
9	M	5	20	R femur	No weight bearing	Yes	Corticosteroids, furosemide, spironolactone, vitamin C, calcium, phosphonic acid
			22	R tibia	Immobile		
			24	L humerus			
			28	R humerus			
10	F	84	96	L femur	Wheelchair; no weight bearing through lower extremities	Yes	Levalbuterol
11	M	6	39	L femur	Immobile	Yes	Not provided
12	F	2	13	L femur	No weight bearing	Yes	Heparin, diphenhydramine, sucralfate
			15	R femur			
			23	R femur			
13	M	97	99	L tibia	Vent-dependent with tracheostomy	No	
14	F	6	24	R femur	Rolling from prone to supine; independent head control in supported sitting	Yes	Metoprolol, hydrochlorothiazide, spironolactone

[a] Medication with potential impact on bone density.

which may involve complex mechanisms described above. Of the 14 children, 13 had a documented decrease in BD, all had residual weakness, and none was ambulatory. None of the children who sustained long-bone fractures was able to support weight through the lower extremities at the time of fracture, suggesting that lack of weight bearing is a significant risk factor, as would be expected. A limitation of the study is its retrospective nature and the very fragile population, limiting our ability to collect related data or further laboratory data. Further studies are required to delineate the cause or causes of decreased BD and decreased bone strength, including histological analysis of bone to examine whether there is osteonecrosis similar to that noted in Gaucher disease or an imbalance between osteoblast and osteoclast activity that could be related to the underlying disease process itself.

With identification of the increased risk of fracture with increased survival with the use of ERT in children with Pompe disease, issues of surveillance and intervention are raised. Incidental identification of a vertebral compression fracture on radiographs in a patient in our series, without the presence of clinical manifestations, suggests that additional screening for such fractures, which would have the potential to become symptomatic or compromise the integrity of the vertebral column over time (e.g., fracture-related kyphosis or scoliosis), is warranted in individuals with Pompe disease.

In considering appropriate imaging studies in identifying decreased BD, it should be noted that at least 40% of bone loss is required before osteopenic changes can be seen on radiographs. Given this limitation (a limitation of this study, also) and the current limitations of DEXA as previously discussed, more sophisticated methods of assessing bone mineral density such as single-energy quantitative CT are warranted, and dual-energy quantitative CT, peripheral quantitative CT, and quantitative long-bone ultrasonography, as they evolve, might yield more relevant information on BD in children.

Based on our clinical experience, we recommend an initial limited bone survey (lateral complete spine, and single AP view of all extremities, and single chest and abdomen with orthogonal views of any positive or suspicious areas) with consideration of DEXA scans at 1 year or older, which is the age at which norms currently exist. Baseline assessment of an individual's BD, with follow-up at clinically relevant points in time, could be useful in clinical management of that individual. More data are needed on the significance and clinical usefulness of information gained from DEXA, as well as from other types of imaging, with a need for more normative data and the potential clinical relevance of changes in DEXA scores and other measurement over time.

Awareness of the risk of fracture and surveillance to allow monitoring of BD, BMD, and characteristics of bone strength over time might allow timely application of

possible treatment or prevention methods such as: avoidance of medications that have the potential to decrease bone density, such as steroids and calciuric diuretics, where possible, physical therapy that includes careful use of exercise and earlier use of supported standing and standing devices that have been shown to be of benefit in other diagnoses [38–41], caution in the application of forces and positioning, and possible consideration of bisphosphonate therapy [5, 42–44]. Further research is needed regarding methods of prevention of, and intervention for, fracture in children with Pompe disease with increased survival with ERT.

Conclusion

The advent of ERT for individuals with Pompe disease has paved the way for the survival of these children that was not possible in the past, and for optimization of motor function, with some children now walking and even running. However, an increased risk of fractures has been identified, perhaps especially in children with a less robust motor response and in those who are not walking and not weight bearing, as shown by this case series, demonstrating the need for careful monitoring and further investigation.

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