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Physical therapy management of Pompe disease

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Pompe disease (Glycogen storage disease type II, GSDII, or acid maltase deficiency) is an autosomal recessive disorder characterized by deficiency of acid α-glucosidase resulting in intra-lysosomal accumulation of glycogen and leading to progressive muscle dysfunction. The natural history of infantile-onset Pompe disease is characterized by hypertrophic cardiomyopathy and profound generalized weakness presenting in the first few months of life, with rapid progression and death usually occurring by one year of age. Late-onset Pompe disease is characterized by onset of symptoms after one year of age, less severe or absence of cardiac involvement and slower progression, with symptoms primarily related to progressive dysfunction of skeletal muscles and respiratory muscle involvement. Recent clinical trials of enzyme replacement therapy have begun to allow greater opportunity for potential improvement in motor status, function, and survival than ever before, with hopes of moving toward maximizing physical function for individuals with Pompe disease. Children are living longer with some achieving independent sitting, creeping, and walking-milestones typically never achieved in the untreated natural history of the disorder. With increased survival, clinical management based on an understanding of the pathology and pathokinesiology of motor function gains importance. This article reviews current knowledge regarding the motor system in Pompe disease and provides an overview of physical therapy management of Pompe disease, including management strategies for individuals on enzyme replacement therapy.

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INTRODUCTION:

Pompe disease (Glycogen storage disease type II, GSDII, or acid maltase deficiency) is an autosomal recessive disorder characterized by deficiency of acid α-glucosidase (GAA) resulting in intralysosomal accumulation of glycogen[1, 2]. Glycogen accumulates in various tissues, most significantly muscle, including cardiac, skeletal, and smooth muscle[1, 2]. The natural history of infantile onset Pompe disease is characterized by hypertrophic cardiomyopathy and profound generalized weakness presenting in the first few months of life, with rapid disease progression and death usually occurring by 1 year of age[1, 2]. Late onset Pompe disease (juvenile and adult onset) is characterized by onset of symptoms after 1 year of age, less severe to no cardiac involvement, and slower progression, with symptoms primarily related to progressive dysfunction of skeletal and respiratory muscles[1, 3, 4]. The advent of enzyme replacement therapy (ERT) has begun to allow greater opportunity for potential improvement in motor status, function, and survival than ever before, with the hopes of moving towards maximizing physical function for individuals with Pompe disease[5-10]. In this article the pathology and pathokinesiology of motor function in Pompe disease, and an overview of physical therapy (PT) management of Pompe disease, are provided. Studies have not previously been published on the use of PT with individuals with Pompe disease, therefore recommendations in this article are based on expert opinion, experience, and evidence from other neuromuscular disorders that have clinical features in common with Pompe disease.

OVERVIEW OF MOTOR INVOLVEMENT:

Pathology of Muscle Weakness:

Myopathy in Pompe disease results from intralysosomal accumulation of glycogen in muscle[1]. Glycogen accumulates primarily in muscle (cardiac, skeletal, and smooth) and the liver, but also in the central nervous system (including anterior horn cells, motor nuclei of the brain stem, and spinal ganglia) and other tissues[1]. Glucose metabolism is normal[1, 2]. Muscle involvement begins with enlargement of muscle fibers as glycogen accumulates in intact lysosomes[11], later followed by muscle wasting, the precise mechanisms of which are unclear[12]. Glycogen accumulation in lysosomes is followed by lysosomal leakage or rupture with accumulation of glycogen in cytosol as well as lysosomes[11]. Lysosomal leakage or rupture also releases hydrolytic enzymes believed to have a role in muscle destruction[11] with degradation of

myofibrils adjacent to glycogen accumulation in the cytosol [12]. Skeletal muscle contraction may cause lysosomes to rupture in muscle more than in other cell types, contributing to the greater relative involvement of muscle[11]. Lipofuscin-mediated apoptosis has been hypothesized to contribute to muscle wasting[12]. With disease progression, "endstage" fibers are left containing "empty" fluid filled space with remnants of myofibrillar and sarcoplasmic material[13]. Large vacuoles are evident in muscle fibers on MRI[14]. Protein catabolism and abnormal protein metabolism may occur, due to or exacerbated by poor nutrition, with more rapid clearance of branched chain amino acids that normally have a role in muscle protein synthesis[15-18]. Muscle function may be impaired by loss of contractile mass, decreased contractile function due to clusters of noncontractile material (glycogen) impeding force transmission by interrupting or displacing myofibrils[12, 19, 20], decreased oxidative capacity resulting in decreased adenosine-5'-triphosphate (ATP) availability for contraction, and impaired innervation[21].

Clinical Presentation and Distribution of Muscle Weakness:

Weakness in Pompe disease is greater in proximal muscles than distal, greater in lower extremities (LE's) than upper extremities (UE's), and generally symmetrical but imbalanced across joints[1]. Muscles may feel firm or hypertrophic in spite of profound weakness[1, 2], especially calf musculature, and sometimes quadriceps, deltoids, and paraspinal muscles.

In the infantile form, progressive, profound, and generalized weakness occurs in neck, trunk, extremities, and facial and oral musculature, with macroglossia (Table 1)[1, 2]. MRI shows diffuse hypertrophy of muscle groups with large vacuoles but without evidence of fatty infiltration[14]. Cardiac involvement is severe with early hypertrophic cardiomyopathy progressing later to dilated cardiomyopathy[1, 2]. Respiratory involvement occurs early due to weakness in diaphragm, intercostals, and accessory muscles of respiration[2], with ineffective cough due to weakness in abdominals. Paradoxical breathing with sternal and intercostal retraction during inspiration may occur due to weakness in abdominal and intercostal muscles[22]. (See Pompe Disease Diagnosis and Management Guideline in this issue for respiratory details).

Table 1

Clinical motor and musculoskeletal presentation in infantile-onset Pompe disease [1, 2]

Weakness: "floppy baby" appearance
- Profound, progressive, symmetrical weakness
- Proximal muscles weaker than distal muscles
- Lower extremities weaker than upper extremities
- Neck and trunk weakness profound
- Facial and oralmotor weakness with myopathic facies
- Respiratory involvement includes weakness in: diaphragm, intercostals, accessory muscles of respiration, abdominals
- Hypertrophic cardiomyopathy progresses to dilated cardiomyopathy

Positional tendencies:
- Hip flexion, abduction, external rotation
- Knee flexion
- Plantarvarus at feet and ankles
- Spinal kyphosis at thoracic and lumbar levels in supported sitting
- Head propped back into extension or falling forward in flexion in supported sitting
- Forearm pronation, wrist flexion, finger flexion
- Sternal and intercostal retraction from paradoxical breathing

Potential secondary musculoskeletal impairments:
- Muscle tightness (hypoextensibility) / contracture:
  - Iliotibial bands (initially seen as lateral thigh groove)
  - Hip abductors and external rotators
  - Hip flexors
  - Hamstrings
  - Plantarflexors
  - Plantar fascia
  - Elbow flexors or extensors (position dependent)
  - Forearm pronators
  - Wrist / finger flexors - hypoextensibility over several joints sometimes accompanied by contracture or hypermobility at individual joints
- Joint contractures
  - Hip flexion, knee flexion, ankle plantarflexion
  - Elbow flexion or extension (position dependent), wrist and finger flexion
- Deformity:
  - Rib cage flattened in anterior-posterior dimension with:
    - Sternal retraction (pectus excavatum)
    - Lower rib flaring
  - Spinal deformity; kyphosis, scoliosis, lordosis
  - Pelvic asymmetry with lateral pelvic obliquity, horizontal pelvic rotation, and anterior or posterior pelvic tilt
  - Hip subluxation / dislocation
  - Plagiocephaly, brachycephaly, or scaphocephaly
- Osteopenia / osteoporosis / fracture

In the late onset form, progressive proximal myopathy occurs with greater variation in distribution, extent, and rate of progression of weakness,even within families[1, 3, 4, 23, 24]. Patterns of muscle involvement are listed in Table 2 [1, 3, 4, 23, 25-27]. With progression, weakness can become profound [7]. CT and MRI of muscles in adults with Pompe disease show atrophy, fatty infiltration, and degeneration [25-27]. Cardiac involvement is not typical in late onset disease but respiratory involvement may be relatively more severe than skeletal muscle involvement and can be the presenting feature, with apparent selective involvement of the diaphragm[1, 4].

Table 2

Clinical motor and musculoskeletal presentation in late-onset Pompe disease[1, 3, 4, 23, 25, 27]

Progressive proximal myopathy

Distribution of weakness variable, but:
- Proximal muscles generally weaker than distal
- Lower extremities generally weaker than upper

Weakness common in:
- Pelvic girdle musculature (hip flexors, extensors, abductors, adductors)
- Scapular stabilizers
- Shoulder girdle musculature (including deltoids)
- Spinal extensors (paraspinals)
- Neck flexors more than extensors
- Abdominals
- Hamstrings
- Quadriceps
- Diaphragm

Weakness may progress to include: bicep brachii, triceps, tongue, and other musculature

* Selective early involvement of hip adductors (especially adductor magnus), parapinals, psoas, semimembranosus, ventrolateral trunk muscles, rectus abdominus, gluteals, vastus medialis
* Later involvement of the long head of the biceps femoris, semitendinosus, and anterior thigh muscles
* Respiratory involvement may be more severe than skeletal muscle involvement, with early involvement of diaphragm
* Relative sparing of tensor fascia lata, sartorius, short head of the biceps, gracilis, vastus lateralis, rectus femoris

Risk of secondary musculoskeletal impairment depends on patterns of muscle weakness and compensation and is usually less than in infantile-onset, but scoliosis and lordosis may occur

Pathokinesiology of Motor Function and Disease Progression:

Pathokinesiology in Pompe disease, as in all motor unit diseases, is characterized by a self-perpetuating cycle in which progressive imbalanced muscle weakness, compensatory movement patterns and postural habits, and the influence of gravity interact in the progression of disability [28, 29]. Weakness in Pompe disease evolves from the primary progressive myopathy described above[1, 2], with possible contribution from anterior horn cell involvement. Patterns of weakness have been described in Pompe disease [1-4, 23, 24, 30-32] and pathokinesiology has been studied in other disorders in which proximal weakness is greater than distal, such as Duchenne muscular dystrophy (DMD)[28, 29, 33-37], a primary progressive myopathy, and spinal muscular atrophy (SMA)[38-42], an anterior horn cell disease. Positioning, postural tendencies, and compensatory patterns of movement in these motor unit diseases are initially determined by the interaction between weakness and gravity, further compromised later by secondary musculoskeletal impairments [28, 29, 33, 43]. Alterations in posture and movement used to compensate for lack of adequate muscle strength include manipulation of the line of gravity to mechanically lock joints or prop body parts up against gravity, use of biomechanical advantage to optimize movement, substitution, altered or compensatory use of muscles in which greater relative strength exists, and the use of momentum to generate greater inertial forces for movement and maximize kinematic efficiency of movement[33, 43]. Compensations are effective in maximizing function but, used persistently, can lead to contracture and deformity that contribute to increasing weakness and disability[29, 35]. Compensations can also limit the use of existing strength by placing muscles at a mechanical disadvantage, compromise length-tension relationships, and limit opportunities to increase or maintain strength, leading to additional disuse atrophy[44]. "Proportional increases" in weakness may occur with growth due to biomechanical disadvantage as height, weight, or mass increase without the ability of the muscles to cope with the increased workload, as in DMD and SMA[40]. Respiratory involvement, and cardiac involvement, if present, can further compromise function and endurance as in other disorders[1, 2, 45, 46], as can undernutrition due to feeding problems from oralmotor weakness[15]

Infantile onset Pompe disease:

Positioning in infantile onset has classically been dominated by the force of gravity in the presence of profound weakness, and includes flexion / abduction / external rotation at hips, knee flexion, and plantarvarus at ankles and feet in supine, prone, and supported sitting[2] (Fig. 1).

Fig. 1. Classic positioning and weakness/hypotonia in infantile onset Pompe disease.

Prone may not be functional because shoulder girdle weakness precludes propping on forearms and neck extensor weakness may prevent head lifting. Some infants may be too medically fragile to tolerate prone, while others with cardiac involvement may show improved O_2 saturations in prone due to relief of pressure on the pulmonary system in prone. In supported sitting, the vertebral column tends to be in kyphosis with the head propped into extension or falling forward into flexion. Minimal antigravity movement may be possible with greater movement usually observed distally in upper and lower extremities.

Compensatory movements used depend on level of residual strength. Phasic, ballistic movements that capitalize on the use of momentum may be more possible than sustained or eccentric movements and may influence strategies for movement. Phasic bursts of shoulder muscle activity, with the use of momentum, may be used to position the hand for function. Phasic bursts of hip flexor activity may be used in attempts at kicking. Difficulty in using sustained or eccentric muscle activity compromises transitional movements, such as weight shifting in sitting, rotation up to sitting from supine, and controlled movement between positions, movements additionally compromised by iliotibial (IT) band tightness, if present. These transitional movements are classically not possible for children with infantile onset Pompe disease[47, 48], and may be avoided initially by children on ERT, but may be possible with supported practice over time. Children on ERT show an initial tendency to scoot in sitting for mobility, avoiding use of quadruped, as is often true of children with weakness or hypotonia.

Scooting in sitting allows phasic use of hip flexors and hamstrings in short bursts rather than the sustained muscle activity in trunk, shoulder and pelvic girdles, elbow extension, and neck extension required for creeping on hands and knees. As higher level activities become possible for some children with infantile onset Pompe disease receiving ERT[6, 8-10], classic compensatory movements used during activities of elevation against gravity with proximal weakness, such as Gower's maneuver, may be observed, although movement from squatting to standing has even been reported without a Gower's maneuver in infantile onset Pompe disease with ERT[5].

Late onset Pompe disease:

Positioning, postural tendencies, and compensatory movements in late onset disease are determined by specific individual combinations of imbalanced muscle weakness around joints, alterations in posture made to compensate for weakness, and secondary musculoskeletal impairments. Many are common to other diagnoses characterized by proximal weakness and are well described in the literature[28, 29, 33, 36, 43, 44]. LE's show a tendency for hip flexion, abduction, and external rotation, both from the influence of gravity and from selective early involvement of adductors and pelvic girdle muscles[3] with relative sparing of sartorius[26]. Posterior trunk leaning is common in standing[3] to put the line of gravity posterior to the hip joint to compensate for weak hip extensors. Increased posterolateral leaning during stance phase of gait and decreased pelvic stability during gait, sometimes described as a "hip waddling" or "waddling gait"[3] is used to substitute for weak hip extensors and abductors on the stance side, and to assist hip flexors via momentum on the swing side. Posterior trunk leaning may be accompanied by spinal hyperextension and lordosis[1, 3], especially if the hip remains in flexion with the pelvis anteriorly tilted, as can occur with significant hip extensor weakness and/or a hip flexion contracture. Quadriceps weakness may result in additional hip flexion, anterior pelvic tilt, and lordosis in upright to position the line of gravity simultaneously behind the hip joint and in front of the knee joint, if sufficient plantarflexion torque is available. Spinal alignment may shift to kyphosis in sitting due to paraspinal weakness[1, 3] and the influence of gravity as posterior leaning compensatory for hip extensor weakness is not needed in sitting. Scapular winging is common and may be pronounced[1, 3]. Gower's maneuver may be used in activities of elevation against gravity, when achieving standing from the floor or when achieving standing from sitting in a chair. Compensatory movements used to assist UE function can include lateral trunk leaning to assist with contralateral shoulder abduction and elbow flexion, posterior trunk lean to assist with

ipsilateral shoulder and elbow flexion, and bimanual assist to position the hand for function. Head movement may be used for momentum and to assist with a variety of movements. Although some selective specificity of muscle involvement has been identified[3, 26], many of the compensatory movements used in other disorders characterized by proximal weakness[36, 44] may also be observed in Pompe disease.

Secondary Musculoskeletal Impairments:

Secondary musculoskeletal impairments occur in accordance with principles of biomechanics and developmental biomechanics[49] in which the application of small forces over time has powerful effects, especially during periods of rapid growth, and in which muscle length is strongly influenced by the number of hours per day that muscles are in shortened or lengthened positions[35, 50, 51].

Muscle extensibility impairments, contracture, and deformity:

Muscle hypoextensibility, muscle hyperextensibility, contracture, and deformity can develop from the chronic alterations in posture and positioning that result from weakness[52] and can further compromising muscle function, effective movement, positioning, and comfort. Contracture and deformity occur in accordance with severity of weakness, age of onset and duration of weakness, extent of imbalanced muscle activity, and intervention used or not used to minimize contracture and deformity[29, 35, 53]. Muscles that cross two or more joints are at increased risk of early contracture[29]. With severe, early weakness, the unopposed force of gravity has the most profound effect on positioning and the development of contracture and deformity, as in SMA[54]. With moderate to mild weakness, muscle imbalance across joints has an increased role in the development of contracture and deformity, as in DMD[29, 35]. Immobilization of muscle from chronic positioning in any diagnosis can lead to changes in fiber length and extensibility, sarcomere number, sarcomere length, length-tension curves, collagen concentration and orientation, ratio of tissue to muscle fiber, stiffness, and changes in ratio of tendon length to muscle belly[50, 51], with muscle plasticity responsive to both deforming and corrective forces.

Positional tendencies in individuals with infantile onset Pompe disease lead to early contracture of IT bands, followed by hip and knee flexion contractures, and contracture of plantarflexors and plantar fascia. Positional tendencies and hypoextensibility may persist even with ERT, typically more pronounced in patients with more weakness at the start of treatment. IT band tightness can create biomechanical limits to active hip adduction and can limit

weightshift and smooth transitions between positions. Asymmetrical IT band contracture can lead to subluxation of the contralateral hip, as in other disorders[55]. Hip and knee flexion contractures can limit active hip and knee extension and further compromise biomechanics in prone and upright. Plantarflexion contractures can compromise foot support and lower extremity positioning in supported sitting, limit possibilities of supported standing, limit effective use of ankle foot orthoses (AFO's), and limit possibilities for function in standing and walking. Decreased head control and movement in infantile onset form can lead to abnormal cranial molding, with resultant plagiocephaly, brachycephaly, or scaphocephaly. Dominance of gravity in supine can lead to A-P flattening of the rib cage. Paradoxical breathing can lead to sternal retraction and pectus excavatum with lower rib flaring from lack of stabilizing activity of abdominal obliques and intercostals[22, 56]. Relative weakness in wrist and finger extensors compared to flexors can lead to hypoextensibility of long wrist and finger flexors across multiple joints, which may be accompanied by hypermobility or contracture at individual joints. Classic areas at risk for abnormal muscle extensibility, contracture, and deformity in the infantile onset form are listed in Table 1[1, 2].

Risk of contracture and deformity is also present in late onset Pompe disease, including scoliosis and lordosis[1], but presence and severity may vary due to greater variation in weakness. Classic compensations, such as spinal hyperextension in standing with posterolateral trunk lean[3] during stance phase of gait or to assist UE function, may be necessary for function as in other motor unit diseases, and cannot be eliminated without eliminating the function they serve[41, 44]. Spinal hyperextension may protect against fixed spinal curves in ambulatory individuals as in other disorders[57]. The risk of spinal asymmetry and malalignment, including fixed spinal deformities such as scoliosis, kyphosis, and lordosis, may increase over time with increasing weakness or may stabilize with skeletal maturity. The risk of neuromuscular scoliosis is greatest in non-ambulatory individuals, influenced by age, rate of growth, and the interaction between weakness, postural malalignment, compensatory movements used to maximize UE function, and the influence of gravity[57].

Osteopenia / osteoporosis:

Osteopenia and osteoporosis have recently been recognized as complications of Pompe disease and osteopenia has been identified in infants as young as 4 months of age[58]. Femoral and vertebral fractures have been identified in patients with infantile onset disease[58] and vertebral

fracture has been reported in late onset disease[59] (see Pompe Disease Diagnosis and Management Guideline in this issue for details regarding ostoepenia and osteoporosis).

Gross Motor Function:

Infants with infantile onset disease historically did not achieve motor milestones of independent sitting, creeping, standing, or walking[1, 2, 47, 48], a fact that is changing with ERT, with some children on ERT now walking independently[2, 5, 6]. In a study of physical disability in children spanning infantile and late onset forms and ranging from age 6 months to 22 years, 2/3 were non-ambulatory, ¾ used a ventilator, and age did not correlate with level of disability[60].

Individuals with late onset disease characteristically experience gradual difficulty with motor function, noted initially in walking, running, and activities of elevation against gravity such as climbing stairs, rising from the floor, getting up out of a chair, lifting the arms overhead[24]. The use of mobility devices such as canes, walkers, manual wheelchairs, and powered mobility are usually added gradually, often used part-time at first, for long distance community mobility or on uneven terrain[24]. Progression of weakness and increased risk of falls may lead to ambulation only possible or practical indoors on level surfaces for short distances in safe environments such as home; with a manual or motorized wheelchair or scooter used in all other environments. Mean age at which use of a wheelchair is initiated has been reported as 46 years[24] and mean age at which ambulation is lost as 50 years[3].

PHYSICAL THERAPY MANAGEMENT:

Physical therapy (PT) management of Pompe disease, as in all motor unit diseases, should provide comprehensive, anticipatory, and preventative management based on an understanding of the pathophysiology and pathokinesiology of disease presentation and evolution, and on individual assessment[29, 44, 61]. The key to management lies in understanding the interaction between the presence, progression, and potential remediation of weakness; the biomechanics of efficient movement; the risks for development of contracture and deformity and strategies for prevention and remediation; the risks and possible remediation of osteoporosis; and function. Muscle weakness presents and progresses in generally predictable patterns with predictable compensations used to cope with weakness[1, 2, 29]. Secondary muscle tightness, contracture, and deformity occur in predictable patterns without intervention[29]. Intervention is focused on breaking or slowing this predictable, self-perpetuating cycle of events whenever possible[28] so that strength and endurance are maximally achieved and maintained, contracture

and deformity are minimized, and compensations can be used to maximize function without leading to increased disability. PT intervention is designed to optimize and preserve motor and physiological function as much as possible within the limits of the disease; to minimize the clinical impact of the disease process; to prevent or minimize secondary complications; to promote and maintain the maximum level of function, functional independence, and participation; to optimize quality of life; and to maximize the benefits of enzyme replacement or other treatments as they become available. PT should address all domains of the World Health Organization (WHO) International Classification of Functioning, Disability, and Health (ICF)[62] as well as the interaction between these domains; and evaluation and intervention should reflect current standards of care and management[63, 64]. Selected PT assessment tools are described in Appendix A of the Pompe Disease Diagnosis and Management Guideline in this issue. PT may be provided in a variety of settings, depending on the needs and preferences of the individual and family (see Pompe Disease Diagnosis and Management Guideline in this issue for details regarding service delivery and funding sources).

Management of Skeletal Muscle Function (Strengthening and Enhancing Motor Function):

Guidelines for muscle strengthening are not established for individuals with Pompe disease. Studies of the effect of strengthening in individuals with Pompe disease have been few, with small numbers, limited to late onset form, and recommend aerobic and submaximal exercise, reporting that submaximal exercise may stimulate the degradation of some of the glycogen that accumulates in the cytosol[15]. and that aerobic exercise combined with optimal nutrition may help clear glycogen from muscle with accompanying gains in strength and function[65, 66]. Concern exists, however, about excessively strenuous strengthening, consistent with precautions in disorders characterized by muscle degeneration in which strenuous exercise contributes to weakness by increasing muscle degeneration[46, 67-71]. Awareness of general precautions with exercise in the presence of myopathy and cardiorespiratory impairment is important as well as the potential, theoretical concern in Pompe disease that excessive muscle contraction could increase leakage of glycogen from lysosomes or cause lysosomal rupture[11] Studies of the effects of strengthening and exercise including strengthening and exercise with ERT are needed. If structural and physiological integrity in muscle is re-established with ERT due to a decrease in abnormal glycogen accumulation, more normal capacity for exercise may emerge. There is early evidence in animals that enzyme replacement may clear glycogen from

cardiac and type I muscle fibers more efficiently and more fully than from type II fibers which may impact strengthening emphasis and results[72]. Until more definitive studies are completed, caution and moderation in exercise are recommended.

Recommendations regarding strengthening of fragile muscles include precautions and guidelines from other degenerative muscle diseases[46, 67, 68, 73-93], with an emphasis on the use of submaximal and aerobic exercise avoidance of excessive resistive and eccentric exercise, use of functional activities for exercise, and appropriate monitoring of cardiopulmonary and respiratory response to activity, to exercise, and even to different positions (especially supine). Monitoring with pulse oximetry is recommended during initial examination and treatment, with changes in status and activity, and as needed based on medical stability. Exercise programs should consider fragility due to possible loss of contractile mass and contractile protein content and the possibility of abnormal force transmission within the muscle cells due to accumulation of non-contractile glycogen[12]. Consideration of physiological fragility should include cardiorespiratory impairment and potentially decreased oxidative capacity resulting in decreased ATP availability for muscle contraction.

Intervention for enhancing muscle function should include strategies to optimize biomechanical advantage for movement, minimize contracture against which weak muscle must work, allow practice and strengthening within limits of physiological stability, avoid overwork weakness, avoid disuse atrophy, use energy conservation techniques, and avoid excessive fatigue (Table 3). Although excessively strenuous exercise should be avoided, gentle submaximal exercise is also believed to be important to allow practice of new motor skills and patterns of functional movement, especially in children; to allow strengthening within physiological limits; to avoid additional disuse atrophy, especially in muscles that might not be used spontaneously because of biomechanical disadvantage and relative weakness compared to other muscles; and to avoid secondary decrease in cardiopulmonary function and deconditioning from inactivity.

Infantile onset Pompe disease:

Weakness in infants can be profound and compromise most antigravity movement. Medical stability and ranges of cardiopulmonary safety should be established prior to initiation of therapeutic activity and cardiopulmonary response to activity and to position changes should be monitored. Self-initiated rests should be respected and rests should be established as needed to insure medical stability, avoid overwork weakness, and conserve energy. Positioning and

support to maximize biomechanical advantage, decrease the impact of gravity, and minimize the development of contracture against which weak muscles must work can allow easier, less strenuous use of weak muscles which might not otherwise be used spontaneously, increasing the possibility of appropriate practice of developmental skills and avoidance of additional disuse atrophy. Strategies of support during functional exercise should include well known motor control principles including control of degrees of freedom to allow permissive conditions for the emergence and practice of movement that might not be possible without support. The buoyancy of water in a tub/pool[94] can provide opportunities for movement while guarding against over-exertion, as long as aquatic precautions are followed, especially regarding medical stability and the effects on respiration of the hydrostatic pressure of water on the trunk. Prolonged exposure to excessively heated pools should be avoided in myopathies, in order to avoid fatigue. Gentle facilitation of movement with active, graded assistance and with assisted practice of movement in all medically safe positions may allow additional practice of developmental skills and strengthening of muscle within physiological limits and may maximize the benefits of ERT as it becomes available. Specific therapeutic activities making use of the above principles can be used to maximize head and trunk control, facilitate weight shift and transition between positions, facilitate sitting skills and floor mobility such as rolling and creeping on hands and knees, and facilitate standing and walking in children with the capability for these skills[5, 6, 10]

Head control can be maximized by support at midline in supine and in gravity minimized upright positions (supported sitting and standing), with facilitation of balanced neck flexion, extension, and rotation within small ranges in which control is possible, with range of movement expanded as possible. Support of flexion positioning in supine and sidelying increases the biomechanical advantage for active use of abdominal muscles, and may increase opportunities for midline hand use, increased use of upper and lower extremities, and sensorimotor exploration in hand to foot play. Trunk control can be maximized by support of an erect spine in supported sitting to increase the biomechanical advantage of spinal extensors which are typically overlengthened and disadvantaged by excessive spinal flexion. Active use of trunk musculature may be facilitated with gentle weight shift away from midline in supported sitting, beginning in small ranges. Support of more normal LE alignment in sitting, rather than flexion / abduction / external rotation (Fig. 2), allows easier weightshift in sitting for more dynamic and functional

sitting, encourages use of trunk and pelvic musculature (Fig. 3, 4), and increases opportunities for transitions to other positions, increasing independent mobility.

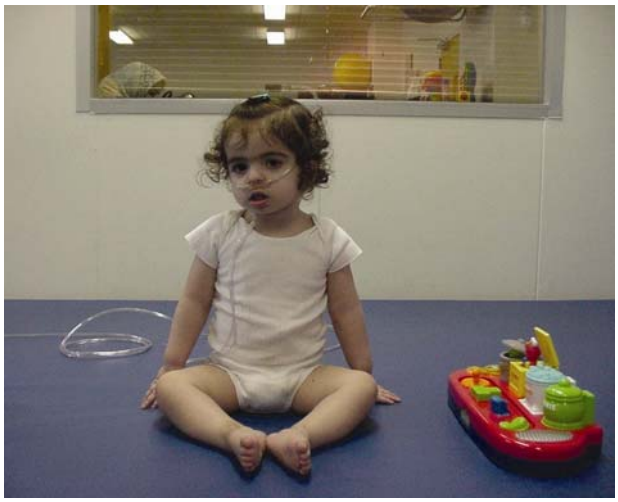

Fig. 2. 14 month old child with infantile-onset Pompe disease on ERT. Sitting posture with straight back, but lower extremities in typical flexion, abduction, external rotation (provides stability but prevents weight shift and transition out of sitting). May lead to scooting in sitting for mobility, rather than creeping on hands and knees, if creeping is not facilitated.

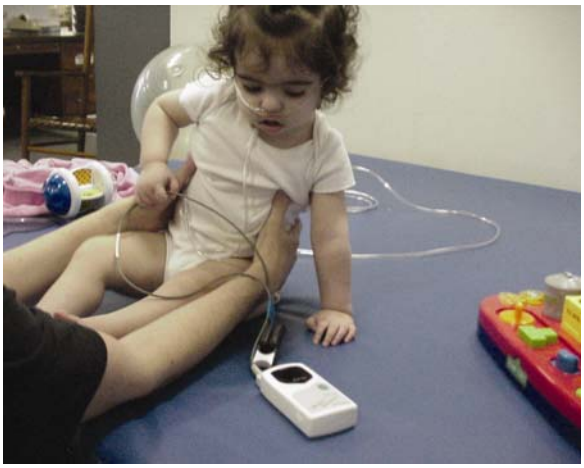

Fig. 3. 14 month old child with infantile-onset Pompe disease on ERT. Facilitation of weight shift, protective extension, and weightbearing through upper extremity in sitting, with lower extremity positioning controlled to allow transition to another position.

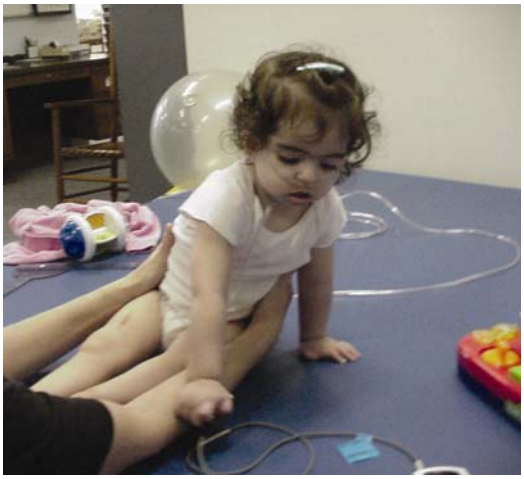

Fig. 4. 14 month old child with infantile-onset Pompe disease on ERT. Stabilization of lower extremities and facilitation of weight shift in sitting for more active beginning trunk rotation, reaching across midline and outside of the base of support, with weightbearing through the other upper extremity.

Facilitation of rolling and transitions between positions may allow the development of functional transitional movement as well as providing opportunities for gentle strengthening. Prone may be possible even for fragile, weak infants, with supervision, with adequate support at the head, upper chest and shoulders as needed, the use of supportive adaptive equipment, and the use of an incline to decrease the impact of gravity. With sufficient strength, as may be possible with ERT or in late onset disease, support of quadruped (Figs. 5 - 7), transitional movements between positions, supported standing (Figs. 8, 9), and walking become possibilities. Functional strengthening activities such as adapted trike riding (Fig. 10) may become possible to provide opportunities for gentle reciprocal lower extremity exercise and to promote lower extremity weightbearing.

Fig. 5. 14 month old child with infantile-onset Pompe disease on ERT. Facilitation of quadruped with support at shoulders and hips.

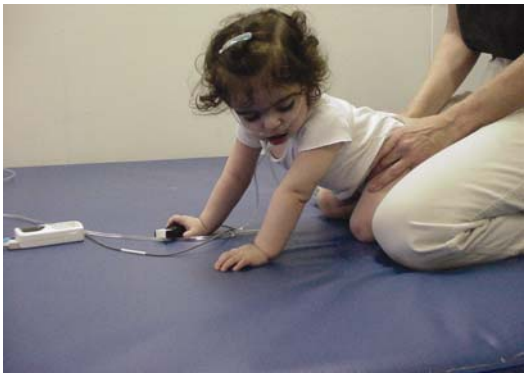

Fig. 6. 14 month old child with infantile-onset Pompe disease on ERT. Facilitation of quadruped with support only at hips.

Fig. 7. 14 month old child with infantile-onset Pompe disease on ERT. Facilitation of forward weight shift and reaching in supported quadruped.

Fig. 8. 14 month old child with infantile-onset Pompe disease on ERT. Facilitation of sit-to-stand and supported standing at a support.

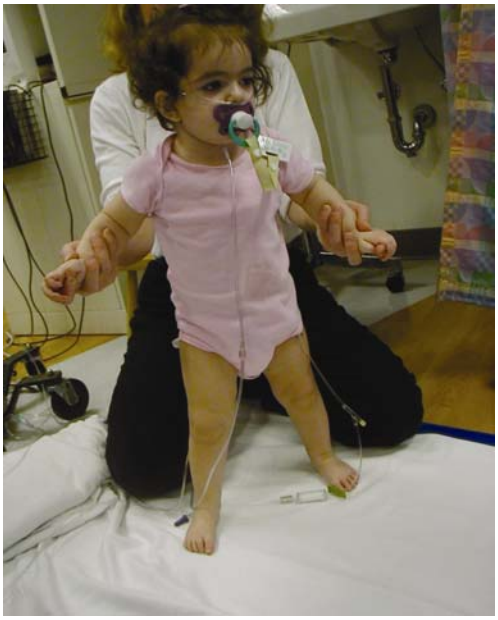

Figure 9: 14 month old child with infantile-onset Pompe disease on ERT. Facilitation of standing with hand support.

Fig. 10. Tricycle: 21 month old child with infantile-onset Pompe disease on ERT. Using adapted trike with shoe-holders.

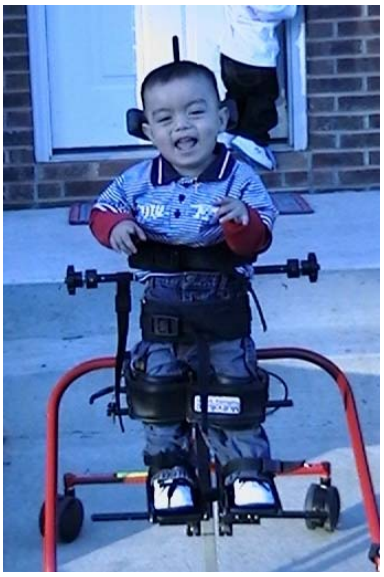

Fig. 11. Stander: 21 month old child with infantile onset Pompe disease on ERT. Stander used for experience in standing, to provide weightbearing in good alignment, and to prevent / minimize contracture into hip flexion, knee flexion, ankle plantarflexion. Elongates gastrocnemius muscles across knee and ankle joints simultaneously.

Infants with Pompe may display an initial aversion to weightbearing through extremities, as is often characteristic of infants and young children with hypotonia and of weakness of any etiology. Aversion of weightbearing may be evident in an avoidance of propping through upper extremities in supported sitting, decreased tolerance of supported quadruped, and astasia in attempts at supported standing. Gentle practice of weightbearing, with adequate support for successful stability and function, can increase active participation in, and functional use of, weightbearing in all positions. Avoidance of weightbearing in quadruped, and preferential use of phasic hip and knee flexion rather than more tonic use of shoulder and pelvic girdle musculature may lead to the spontaneous use of scooting in sitting rather than creeping for mobility. Quadruped and independent creeping on hands and knees have been achieved by some children on ERT and can become a spontaneously used means of mobility prior to the achievement of walking[5, 6, 10]. Quadruped can be supported by providing adequate support and facilitation (Figs. 5-7), providing opportunities for practice of more normal kinematics and strengthening at shoulder and pelvic girdles and in the trunk. Tolerance of weightbearing in standing can be built by providing experience and support in standing in PT sessions (Figs. 8-9) and home programs, and may be supported by the use of standers where appropriate (Fig. 11). Coordination with the rest of the team should occur regarding bone density and integrity, levels of osteoporosis, hip joint status, and potential precautions regarding weightbearing.

Late onset Pompe disease:

For older individuals, and those with more residual strength, gentle submaximal and aerobic functional exercise, such as swimming and cycling without excessive resistance, with active assist as needed , and functional activities, performed with respect for the limitations of cardiopulmonary and muscular endurance are generally considered beneficial[15, 46, 65-68, 94, 95], and may maximize the benefits of ERT as it becomes available. Excessive resistive and eccentric exercise is considered contraindicated in most neuromuscular diseases characterized by muscle degeneration, although debate exists over details of appropriate guidelines for many disorders[67-69, 78, 96]. Submaximal, graded, regularly scheduled exercise is considered beneficial in optimizing strength and avoiding additional disuse atrophy[46]. Excessive stairclimbing is generally considered an activity to avoid in disorders characterized by muscle degeneration because of excessive concentric demands when ascending stairs and excessive eccentric demands when

descending stairs[68]. Energy conservation techniques assist in avoiding excessive exertion which may lead to overwork weakness.

Table 3

Physical therapy management – movement and strengthening

Establish medical stability and ranges of cardiopulmonary stability

Optimize biomechanical advantage for movement:
- Provide positioning and support to increase biomechanical advantage
- Optimize influence of gravity
- Use positioning that optimizes length-tension relationships in muscle
- Minimize contracture against which muscles must work
- Control degrees of freedom to provide permissive conditions for optimal movement and for the emergence of new movement

Allow practice and gentle strengthening within limits of physiological stability, following precautions and guidelines from other degenerative muscle disease:
- Use submaximal, aerobic exercise
- Use active assistance where needed
- Avoid overwork weakness and excessive fatigue
- Avoid excessive resistance during exercise
- Avoid eccentric exercise
- Establish rests as appropriate and respect self-initiated rests
- Use appropriate cardiopulmonary monitoring during exercise

Avoid disuse atrophy

Use energy conservation techniques

Management of Respiratory Muscle Function and Pulmonary Status:

Respiratory / pulmonary management should follow current established guidelines for neuromuscular disorders[97], and specific guidelines for Pompe disease as outlined in the Pompe Disease Diagnosis and Management Guideline in this issue. Respiratory and pulmonary care is supported by PT management of respiratory / pulmonary function, including recognizing the effects of positioning on respiratory function[98], maximizing respiratory function and efficiency[99-101], use of airway clearance and pulmonary hygiene techniques (potentially including chest PT, active cycle breathing, autogenic breathing, positive expiratory pressure and flutter, intrapulmonary percussive ventilation, high frequency chest wall oscillation (HFCWO) with the use of vests [102], manually and mechanically assisted coughing with a mechanical in-exsufflator

[103], and appropriate exercise, depending on age, level of involvement, and capabilities of the individual)[104], maintenance of rib cage mobility, and inspiratory muscle training as appropriate and as established in other neuromuscular disorders[105]. Monitoring of oxygenation levels in different positions, and during activity and exercise with pulse oximetry is recommended.

Prevention of Secondary Musculoskeletal Impairments:

Secondary musculoskeletal impairments, including contracture and deformity, should be prevented by counteracting deforming forces in accordance with principles of developmental biomechanics[49] using gentle forces over time with daily stretching, correction of positioning, splinting and orthotic intervention, provision of adequate support in all positions, support in standing as appropriate, use of adaptive equipment and assistive technology, and education of patients and families (Table 4)[53, 106]. Increased incidence of osteopenia and osteoporosis, and increased risk of fracture[58] must be considered in application of forces. Interventions with the potential to contribute to bone strength and integrity, including weightbearing in PT and standing devices, shown to be associated with increased bone density in individuals with neuromuscular diagnoses[107-111], should be considered, but even normal forces have the capacity to lead to "fragility or low energy fractures" in osteoporotic bone[109, 111-113], and care must be taken in force application. The natural evolution, and effective principles for treatment, of contracture and deformity in neuromuscular disorders are well established[29, 106, 114, 115] and should be followed in intervention for individuals with Pompe disease.

If adequate strength for more normal and complete antigravity movement is available early through ERT, and if motor milestones are achieved at relatively typical ages with a normal amount of movement throughout the day, the forces that lead to contracture and deformity may not occur and prevention of secondary musculoskeletal impairment may occur spontaneously through normal movement, as in typically developing children. However, monitoring and protection of the musculoskeletal system during ERT is critical so that secondary impairments such as contracture and deformity do not occur and limit the benefits of enzyme replacement.

Stretching should be initiated preventatively and done daily when there is a risk of contracture due to weakness and chronic positioning and is best augmented by follow-up positioning including positional supports, splints and orthotic devices, and adaptive equipment[44, 53, 116, 117]. Stretching should include areas identified by individual assessment and areas of classic risk including hip flexors, IT bands (Fig. 12), tensor fascia lata, hamstrings, long and short

plantarflexors, posterior tibialis, plantar fascia, forearm pronators, and long wrist and finger flexors; with isolated stretching into hip and knee extension and ankle dorsiflexion. Stretching into ankle dorsiflexion should be done with the knee flexed and extended. A stretching program is easier to establish as part of the daily routine if it is begun before muscle tightness / contracture is established and before stretching is painful. Stretching should be done gently and physiologically, with an awareness of the risks of "fragility or low energy fractures"[109, 111-113] in the presence of ostopenia, in a child friendly way, with the child "in charge" of the stretch whenever possible, with comfortable tolerance achieved during stretching, and with adequate age appropriate entertainment during stretching and all therapeutic activities.

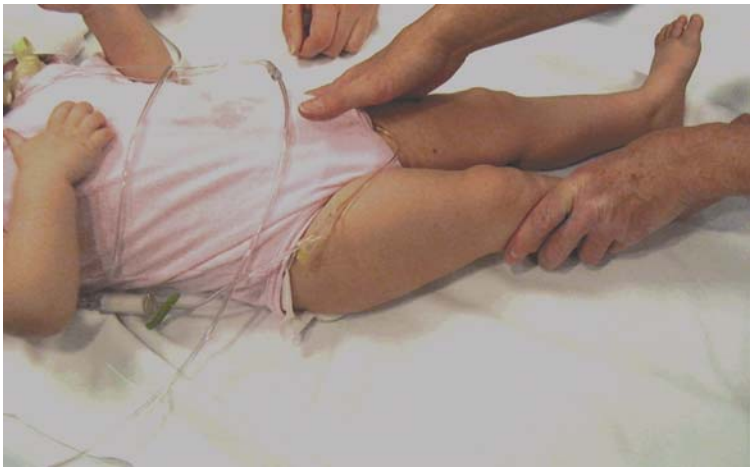

Figure 12: assessing / stretching iliotibial band

Thigh binders (Fig. 13), positional support to prevent hip abduction and external rotation in bed and in infant seats, adductor pads in adapted strollers and in wheelchairs, and gentle daily stretching (with each diaper change in infants) can be used to prevent IT band contracture.

Figure 13: thigh binder
For preventing / minimizing iliotibial band contractures

Prevention of hip and knee flexion contractures includes gentle daily stretching and prevention of chronic positioning in hip and knee flexion with the use of positional support in bed, and the possible use of knee extension splints, floorsitters, elevating leg rests on adaptive seating systems and wheelchairs, and support in standing including the use of standing devices (Fig. 11).

Daily stretching for prevention of plantarvarus contractures should be augmented by prevention of plantarflexion in bed and in adaptive strollers, mobility devices, and wheelchairs, with the use of AFO's (Fig. 14) at the first sign of plantarflexor hypoextensiblity. Use of AFO's at night, shown to be effective in other motor unit diseases[53, 106], may be helpful in preventing plantarvarus contracture and deformity. AFO's may be used in conjunction with thigh binders or knee immobilizers for improved overall lower extremity positioning and muscle elongation (Fig. 15). Serial casting may be used to minimize or correct plantarflexor contracture as long as the weight of the casts is not contraindicated in terms of osteoporosis or constraint of function.

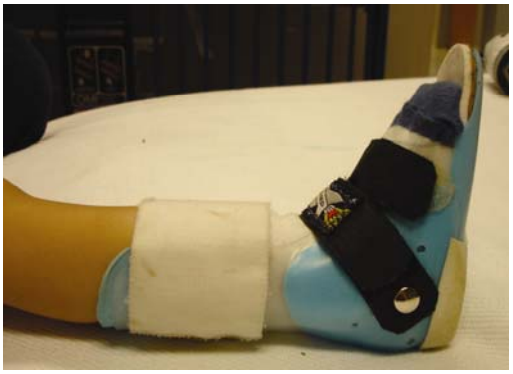

Fig. 14. AFO's (ankle foot orthoses) To prevent / minimize plantarflexor hypoextensibility. To provide improved distal support and alignment for standing / supported standing.

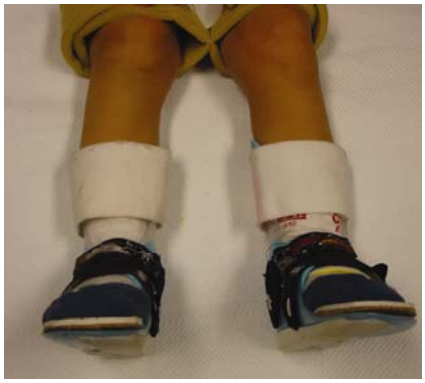

Fig. 15. AFO's and thigh binder used simultaneously to optimize overall lower extremity alignment.

Measures to prevent and reduce contracture and deformity require diligence over time and are important to minimize the resistance and biomechanical disadvantage against which weak muscles must work and to allow motor function and progression. Consideration must be given to the number of hours per day that a muscle is in a shortened position, as this will determine the risk for the development of contracture and deformity as well as determining successful prevention[50, 51].

Adaptive equipment and orthotic intervention:

Adaptive equipment and orthotic intervention can be used to support function, provide positioning to control contracture and deformity, and allow changes in position and pressure relief for maintenance of skin integrity.

Orthotic intervention may include AFO's (Fig. 14) for prevention of plantarflexion contractures[53], thigh binders (Fig. 13) for prevention of IT band contractures, and wrist/hand/finger splints to prevent shortening of long wrist/finger flexors over multiple joints and flexion contracture at the wrist or in individual finger joints. Knee extension splints may be used to prevent knee flexion contractures and maintain hamstring extensibility.

Seating systems in adapted strollers or wheelchairs are used to assist in preventing or minimizing contracture and deformity, especially spinal deformity, and should include solid seat, solid back, hip guides, lateral trunk supports, knee adductors, and head support as needed. Head support should be in place if the seating system is used during transport in a motor vehicle. Adapted car seats and specialized seat belts, harnesses, and vests[118] can be used for safe support in vehicles, and those designed for infants with poor head control[119] should be used for safe transport of fragile infants.

Supported standing may be beneficial in neuromuscular disease, for prevention or minimization of osteoporosis[107-111, 120, 121] as well as for contracture control. Supine standers (Fig. 11) may be most helpful for infants and children with poor head control, G-tubes, and those in whom excessive pressure on the chest from a prone stander could compromise pulmonary or cardiopulmonary function. Hydraulic standers may be optimal for older children and those with better head control. Prone standers may be beneficial for those in whom the added weight of the body assists in providing a more comfortable and effective stretch into hip and knee extension. Power standing capability may be optimal for those who use motorized wheelchairs. Standers should be tried before purchase to insure that the optimal stander for an individual is identified.

The use of positioning, splinting, and standing devices should be coordinated with medical specialists in pediatrics, pulmonary medicine, cardiology, and orthopedics in consideration of potential contraindications in terms of cardiac or pulmonary status, osteoporosis, the risk of fracture, hip subluxation or dislocation, and prohibitive hip and knee flexion contractures.

Table 4

Physical Therapy Management - Prevention of Contracture and Deformity

Optimize alignment and positioning

Minimize deforming force of gravity

Stretching:
- Passive stretching should be done daily and is best augmented by:
  - Active assistance if possible
  - Joint mobilization as needed
  - Modalities as appropriate (gentle heat, warm bath)
- Stretch the structures that are at risk, and those identified by individual assessment:
  - Iliotibial bands
  - Hip and knee flexors
  - Hamstrings
  - Plantarflexors
  - Plantar fascia
  - Elbow flexors
  - Forearm pronators
  - Wrist/finger flexors
  - Anything else at risk by exam: individual joints, rib cage, spine

Follow up with active movement as possible and prolonged positioning:
- Orthotic intervention (orthoses, casting)
- Lower extremity binders (thigh binders)
- Knee immobilizers / knee splints
- Spine jackets
- Wrist/hand/finger flexor splints
- Standers or wheelchairs with standing capability
- Adaptive seating and mobility devices (specialized strollers and manual and motorized wheelchairs with custom seating and motorized positional changes)

** The number of hours per day in a given position determines the development / prevention of contracture and deformity **

** Standing may be important to minimize contracture and osteopenia/osteoporosis

Function:

At every age, and every stage, appropriate function and maximal levels of independence, should be supported as allowed by levels of medical stability, including participation in all aspects of life in which the individual is interested. Functional developmental activities and participation as well as maximal independence in activities of daily living should be supported. Practice, adaptation for function, and family education should be included. Appropriate adaptive

equipment and assistive technology should be used to assist in activities of daily living, to maximize function and functional independence, to provide safety in transfers and transport for access. Technology may be the key to function and freedom in many situations, including motorized mobility (with power positioning controls such as tilt, recline, elevating leg rests, seat elevation, seat to floor mobility, and standing) with ventilator trays if needed; power lifts (including portable patient lifts, ceiling lifts, stand-pivot lifts, stairclimbers, vans lifts); computers (including voice activated systems, adapted keyboards, microswitches, hand held computer devices); internet access; environmental control units; ramps and portable ramps; bathing and bathrooming equipment that fosters ease and independence such as specialized bath and shower chairs, hand held showers, roll-in showers; power operated adjustable beds with hand held remote and alternating pressure pad with pump for pressure relief and maintenance of skin integrity; and all aspects of emerging technology. Motorized mobility should be considered early enough to allow functionally independent mobility at developmentally appropriate ages, reported as early as 20 months of age in SMA[122-125]. Recommendation and training in the use of assistive technology at home, school, and work are important. Driving may be appropriate.

CONCLUSION:

The clinical manifestations of Pompe disease are beginning to change with the advent of ERT (Fig. 16) with greater opportunity for potential improvement in motor status, function, and survival than ever before[5-7]. With the potential of ERT as a treatment for Pompe disease, provision of comprehensive clinical management is important in maximizing clinical and functional benefits of ERT. The purpose of this article is to increase the understanding of the pathology and pathokinesiology of motor function in Pompe disease, and to provide an overview of physical therapy management. Physical therapy is an important component of management and should be included in the multidisciplinary team for care for individuals with Pompe disease.

Figure 16. Child with infantile onset Pompe disease on ERT climbing stairs – greater potential for improved function emerging.

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