Overview of Late Onset Pompe Disease

- Pathophysiology
- Molecular Genetics
- Clinical Problems
- Treatment Paradigms
Pompe Overview

- estimated at 1 in every 40,000 births
- Caused by a gene mutation
- Product is an enzyme alpha-glucosidase (GAA)
- GAA breaks down glycogen (stored glucose)
- May see reduction or complete absence of GAA
- Inherited in autosomal recessive fashion
Pompe Overview

- estimated at 1 in every 40,000 births
- 70 different mutations in GAA gene known that Pompe disease
- Variable age of onset
- Severity of the disease and the age of onset are related to the degree of enzyme deficiency.
Pompe Overview

- Excessive amounts of glycogen accumulate everywhere in the body,
- Heart and skeletal muscles most affected
- *infantile Pompe disease* shows complete absence of GAA = fatal.
Pompe Overview

- In first months of life see feeding problems
- poor weight gain,
- Generalized muscle weakness & “floppiness”
- Respiratory difficulties with pneumonia.
- Cardiomegaly
- enlarged tongue.
- Death usually from cardiac or respiratory failure before first birthday.
Pompe Overview

• DNA studies and muscle biopsy will confirm diagnosis and distinguish Pompe from Duchenne muscular dystrophy (DMD), severe limb girdle MD, congenital myopathies or mitochondrial disorders (which can appear clinically similar)
Late Onset Pompe

- partial deficiency of GAA.
- onset as early as first decade
- as late as the sixth decade
- Diffuse muscle weakness
- Respiratory compromise or failure
- The heart may be involved (not grossly enlarged)
Late onset Pompe

- Late onset Pompe confirmed by DNA screen or measuring levels of GAA activity in blood (100% accuracy).
- Family members should be tested and referred for genetics consultation.
- Carriers are identified by DNA mutation analysis.
Muscle Biopsy Results:

- Degenerating atrophic fibers
- Vacuolar myopathy
- Some regenerating fibers
- Connective and fatty tissue infiltration
- Excess glycogen storage
- May be normal in mild case
Dystrophin stain: Normal
## Early vs Late onset Pompe

<table>
<thead>
<tr>
<th></th>
<th><strong>Early</strong></th>
<th><strong>Late</strong></th>
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<tbody>
<tr>
<td>Clinical Onset</td>
<td>birth</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; - 6&lt;sup&gt;th&lt;/sup&gt; decade</td>
</tr>
<tr>
<td>GAA activity</td>
<td>absent</td>
<td>Decreased to varying degrees</td>
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<tr>
<td>Pulmonary</td>
<td>Severe compromise</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Severe with cardiomegaly</td>
<td>Variable, no cardiomegaly</td>
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<tr>
<td>Muscle biopsy</td>
<td>Severe glycogen accumulation</td>
<td>May be normal in mild cases</td>
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<tr>
<td>Life Expectancy</td>
<td>Less than one year</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; to 6&lt;sup&gt;th&lt;/sup&gt; decade</td>
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Pathophysiology of Pompe

Gene mutation

Absent or decreased GAA

Accumulation of glycogen

Cascade of events leading to muscle fiber injury and degradation

Cycles of degeneration \(\Rightarrow\) regeneration

Cell death (replacement by fat & connective tissue)
Clinical Management

Late Onset Pompe Disease
Pattern of weakness in Pompe

- Proximal weakness greater than distal (UE/LE)
- LEs weaker than UEs
- Hip extensors weaker than flexors
- Knee extensors weaker than flexors
- Ankle dorsiflexors weaker than plantarflexors

Wokke JJ, et al: Clinical Presentation in Late Onset Pompe Disease: A One-Year Prospective Cohort Study *Neurology* 2007 (submitted)
Pompe Postural Adaptations

- lordosis
- shoulder retraction
- knee extension
- equinus posturing

- Progressive increase in toe walking to compensate for progressive increase in lumbar lordosis
Pompe Postural Adaptations

- Trendelenberg gait/ Gluteus medius lurch (compensates for hip abductor weakness)
- Increasing postural challenges due to hip extensor and knee extensor weakness
- Increased difficulty maintaining balance
Transition to Wheelchair

Age to wheelchair variable
Common in Pompe patients older than 50 years
May be too weak to use manual chair
Contractures: a consequence of static positioning
Knee contractures

[Graph showing cumulative percent with knee flexion contracture vs. years to/from wheelchair reliance, with lines for ≥5° contracture and ≥15° contracture]
Elbow Flexion contractures

Graph showing cumulative percent with elbow flexion contracture over years to/from wheelchair reliance.
Osteoporosis in Pompe

- May lead to pathologic fractures
- Increased susceptibility to trauma
- Treat with Ca++ and bisphosphonates plus nutrition
- ?Miacalcin
- Weight bearing exercise
Severe Scoliosis is not common in late onset Pompe
Problems Associated with Spinal Deformity

- Poor sitting balance
- Difficulty w/ upright seating & positioning
- Pain
- Difficulty in parent / attendant care
- Exacerbation of underlying restrictive pulmonary disease
Spinal Fusion / instrumentation

Curve severity
20-40 degrees optimal

FVC > 40% predicted
Spinal Fusion only effective treatment of neuromuscular scoliosis.
Respiratory Muscle Weakness and Fatigue

- **Expiratory** muscle weakness produces ineffective cough, problems clearing secretions, increased infections
- **Inspiratory** weakness hypoventilation / hypercarbia → Respiratory failure
Pulmonary

• At each clinic visit, monitor forced vital capacity
• Maximum inspiratory and expiratory airway pressures
• Good review of systems
Signs of impending respiratory failure

- FVC < 20-25% predicted
- MIP < 25-30 cm H₂O
- Check end tidal CO2 or ABG: PaCO₂ > 55
Treat with Non-invasive ventilation:

**BIPAP** (bimodal positive airway pressure)
Cardiomyopathy in Pompe

- Clinically significant cardiomyopathy is common in Pompe
- Fibrosis posterior wall left ventricle
- Myocardium exhibits abnormal contractility
- Purkinje abnormalities lead to tachyarrhythmias
Cardiomyopathy in Pompe

- Regular monitoring with:
  - ECG
  - Echo
  - Holter monitor
Cardiomyopathy in Pompe

- Treatment with:
  - Digitalis
  - Afterload reduction (ACE inhibitors)
  - Anti-arrythmics
Resistive Strengthening Exercise in Pompe

Scant literature

Challenges

• Weakness is progressive
  • slow progression of weakness?
  • increase strength?
  • variable progression
Challenges

- Relative rarity of individuals with Pompe
- Problem of combining disorders, even those with similar clinical picture (LGMD)
Limitations of Past Studies

- Few study subjects with different NMD
- Variable control groups: opposite limb, able-bodied, NMD
- Strength measurement method
- Protocol and duration of study
- Effect on function
In Rapidly Progressive NMD
Vignos et al (1966)
deLateur et al (1979)

- Small n, no control group
- Resistance exercise may have slowed the progression of weakness
- No strong evidence for increased strength
In Slowly Progressive NMD

- Six studies to consider

- High-resistance weight training
- Benefits only when baseline strength >15% of normal
Aitkens et al (1993)

- Moderate resistance training, 12-week home program
- modest increased strength of knee extensors/elbow flexors
- non-exercised limb had similar increases
- no evidence of overwork
Kilmer et al (1994)

- High resistance, 12-week home program
- No additional benefits compared to moderate resistance protocol
- One isokinetic measure (eccentric elbow flexion PT) significantly decreased

- Randomized clinical trial in HMSN/MMD
- Six month training of knee extensors
- Moderate improvement in KE strength of HMSN subjects
- No changes in functional ability or timed motor performance
- No untoward effects

- evaluated whether adherence to high-protein and low-carbohydrate nutrition and exercise therapy (NET) slowed progression
- 34 patients treated for periods of 2-10 years
- Pre-NET rate of muscle function deterioration, was compared to post-NET rate.
- Difference was -0.29 (95% CI -0.19, 0.39) (P < 0.0001).
- Conclusions: NET can slow deterioration
Resistance Exercise Recommendations for Pompe Patients

• May be beneficial if weakness not severe
• High-intensity has no advantage over moderate resistance and may cause more harm
PRECAUTION: Overwork Weakness and Eccentric Contractions
Overwork Weakness

- Controversial
- Reported only in case studies in humans
- Is shown in animals by exhaustive exercise
Kilmer et al (2001)
Eccentric protocol in myopathic subjects
Eccentric contraction protocol
Creatine kinase response
Considerations for Future Resistance Training Studies in Pompe

- Will need to be multicenter
- Comparisons to matched controls with Pompe
- Matching should consider severity of weakness and relative activity level
- Quantitative measures of strength
Considerations for Future Resistance Training Studies

- Functional performance measures (both objective and subjective) are critical
- Type of exercise training (isometric/dynamic, concentric/eccentric) should be precisely defined
- Separate effects of neural adaptation from muscle fiber hypertrophy --> need at least 6 months training
Maximizing Quality of Life with Rehabilitation Interventions for Patients with Pompe Disease

Other Rehabilitation Considerations and Management Principles
What is Quality of Life (QoL)?
Defining the “issues”

- Quality of life is a vague and ethereal entity, something that many people talk about, but which nobody very clearly knows what to do about.

  - Campbell, in The Quality of American Life
Quality of Life?

- “An individuals perception of their position in life in the context of the culture and value systems in which they live, in relation to their goals, expectations, standards, and concerns”  WHO, 2001
**Dimensions of QoL**

- Dimensions that are most important in determining quality of life are:
  - Physical and material well-being
  - Material well-being and financial security
  - Health and personal safety
  - Relations with other people
  - Relations with spouse
  - Having and rearing children
Dimensions of QoL

- Relations with parents, siblings, or other relatives
- Relations with friends
- Social, community, civic activities
- Helping and encouraging others
- Participating in local and governmental affairs
- Personal development, fulfillment
- Intellectual development
Dimensions of QoL

- Understanding and planning
- Occupational role career
- Creativity and personal expression
- Recreation
- Socializing with others
- Passive and observational recreational activities
- Participating in active recreation
Comment

- These dimensions are NO different for people with Pompe Disease or other disabling conditions
In our QoL studies in NMD, what have we found?

- “I would rather have 15 minutes of wonderful, than a lifetime of nothing special”
- *Albert Einstein*
Factors that impact QoL in Pompe

- Distribution of weakness
- Severity of weakness
- Presence of cognitive effects
- Speech and swallowing
- Labored or restricted breathing
Milder forms of Pompe

- may go unnoticed by others...yet can create tremendous disability
More Clinical Paradigms

Other Suggestions to Help Improve QoL for your Pompe Patients
Apply **Multidisciplinary Management**

- Physician
- Nurse
- Physical and Occupational Therapists (PT/OT)
- Speech-Language Pathologists (SLP)
- Respiratory therapist (RT)
- Social worker (MSW)
- Dietician (RD)
Patient Care Team

Pompe Disease is Treatable!!

Physician (neurology/physiatry)
Coordinates
Overall Care Plan

Physical/Occational Therapists
Speech Language Pathologist

Clinical Nurse Specialist
Social Worker
Psychologist
MDA PSC

Consulting Physicians
Pulmonologist
Orthopedic Surgery
GI Surgery
Information is Power

• Make sure diagnosis is correct:
• Refer to genetics!
• An informed patient is an empowered patient
• Explain all the treatment options
• Allow patient and family to grieve and accept (Kubler-Ross stages)
• Trial of Myozyme!!
Correcting biomechanics

- Weakness
- Abnormal gait
- Lordotic posturing
- Dyspnea
- Fatigue
- Cramping
Ordering Therapy Modalities

- Stretching/bracing
- Pool therapy for exercise
- Adaptive devices
- Lifts, bed, cushions
- Speech and swallow eval
family/psychosocial issues

• are parents or siblings depressed?
• Is the child adapting in school?
• Is the adult being accommodated at work?

REMEMBER THE ADA!!!
Other issues

• Weight control
• Good Nutrition
• Educational assistance: IEP
• Appropriate and timely surgical interventions
SURGERIES?

- Hip flexor lengthening
- IT band release
- TAL
- +/- Post.Tib lengthening
Prolonging Ambulation

- Timely surgery, appropriate bracing, may extend ambulation by many years
- Make sure this will work for the patients given situation (i.e., work or school, etc)
Wheelchairs

Assess functionality and safety of gait!!

Wheelchair should be well fit and adaptable: consult with an OT or PT who specializes in WC fitting
Predicting Transition to Wheelchair: Timed Motor Performance may help

- In DMD Time to walk 30 feet
  - < 6 sec → > 2 years to chair
  - 6-12 sec → 1-2 years to chair
  - > 12 sec → < 1 year to chair
When to Rx a wheelchair in adult Pompe?

- Don’t wait until patient falls and breaks hip
- May need both manual and electric
- Medicare regulations are arduous!!
- Scooters are not as useful
Contractures

• What to do about them?
  Nothing, if they are not causing a problem
• Rarely painful
• May make positioning difficult
• Related to loss of strength
Dysphagia in Pompe

- SLP to do clinical evals
- Modified Barium Swallow (MBS)
- Flexible Endoscopy (FEES)
- Texture modification
- PEG when dysphagia severe: do early enough to avoid surgical complication and “wasting”: consider work of breathing
**Dysphagia**

- Deep pharyngeal neurostimulation (DPNS)
- Vita-stim (trials on-going)
- Texture modification
Despite what you’ve been told... may be a big problem for people with Pompe

- Pain is a common problem in NMD
- There are important differences between different NMD groups on the nature and scope of pain and its impact
- More research is needed – especially in Pompe!!
- Need more effective treatments for NMD-related pain
Types of pain in Pompe

- Muscular/cramping
- Musculoskeletal
- Psychological – adapting to disability
### Possible Mechanisms of muscle cramping and pain in Pompe

- Impaired **cell signaling**
- Increased **oxidative stress** (secondary to excess glycogen)
- **Muscle ischemia** (due to interruption of microvasculature by glycogen excess)
Proposed Mechanisms for Myofiber Cramping and Pain in Pompe

- Impaired metabolic capacity
- Excess glycogen
- Mechanical disruption of cell
- Ischemic Pain
- Oxidative Stress
- Impaired homeostasis
- APOPTOSIS / NECROSIS

GAA absence

1. Impaired metabolic capacity

SG - YES
γSG - NO
others - ??

Mechanical disruption of cell
Excess glycogen
Cell Oxidation
Cramping and pain
Musculoskeletal Pain

- We examined health-related QoL and pain in NMD using SF-36
- Assesses pain severity using Bodily Pain scale
- 1,432 participants
- normed with nondisabled adults
• Frequency and severity of musculoskeletal type pain reported in NMD was significantly greater than levels of pain reported by the general United States population and was comparable to pain reported by subjects with osteoarthritis and chronic low back pain.
In NMD, like the general population, there is a significant correlation between pain and depression. This creates fatigue, sleep disturbance, loss of vitality, and decreased social interactions.
Palliative and Hospice Care in Pompe

- He who would teach men to die would at the same time teach them to live.”

Michel de Montaigne
Poor Prognostic Indicators in Pompe

- bulbar involvement with dysphagia and recurrent aspiration
- Congestive Heart Failure refractory to medication
- Older age and co-morbidity
- CO2 retention and/or hypoxemia
Palliative Care = Total Symptom Management

- Treat patient with the goal of relieving the symptoms
- Do not worry about addiction
- Make sure your goals match the patient’s goals and expectations
- Consult if you are not comfortable or able
Pain Management

- NSAIDs (i.e.: Celebrex)
- Tylenol
- Mobility/stretching
- Pressure relief equipment
- Treat depression!
Pain Management

- Define the type of pain: musculoskeletal? Psychological? Both?
- Treat spasticity: baclofen (Lioresal), tizanadine (Zanaflex)
- Neurontin helps with spasticity AND pain
- Use narcotics if needed!! Concern for addiction is pointless – but watch breathing and bowels
Cannabis

• Dries up mouth, alleviates pain and spasticity
• Improves appetite, improves sleep/mood state
• Strong anti-oxidant
• Neuroprotective
• Low toxicity, well-tolerated
• May be eaten or vaporized
• KNOW AND FOLLOW THE STATE LAW
End Stage Mobility Issues

- Hoyer lift
- Electric hospital bed
- Pressure relief mattress
- PT/OT in home safety eval
End of life Planning

• Have “Do Not resuscitate” order signed and readily available
• Avoid 911 calls if possible
• Consult and get in to Hospice program early
• Plan these things out with family’s input
Ethical Considerations

- Patients should direct their care. Clinicians provide information and options and be supportive, not directive
- Dying with Pompe or any NMD should be peaceful and pain-free
Physician Assisted Suicide in advanced Pompe?

- Goes against the Oath of Hippocrates
- Has huge moral and ethical implications
- If patient requests this, then re-evaluate the care they are getting
Acknowledgements

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The End! (phew!)

• Thanks for attending
• E-mail any questions:
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