Late-Onset Pompe Disease: A Review

Omar Jawdat, MD
Neuromuscular Fellow
University of Kansas Medical Center
6/27/2014
Case:

- CC: 40 y/o male with bilateral leg weakness
- HPI: 2011 weight loss 25 lbs over 1 year
  - June 2012 SOB on exertion → at rest
  - Jan 2013 difficulty climbing stairs, difficulty getting out of chair
  - No complaint of arm weakness or ocular symptoms
  - No chewing difficulty, choking or slurring
## Examination

### Motor:

<table>
<thead>
<tr>
<th>Action</th>
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<th>Left</th>
<th>Action</th>
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Background

- Late-Onset Pompe disease (LOPD) AR
- Prevalence of LOPD 1/28,000 to 1/57,000
- First described in 1932 by Dutch pathologist J.C. Pompe
- Lysosomal glycogen accumulation due to acid alpha-glucosidase (GAA) enzyme deficiency
- Progressive degeneration of skeletal and respiratory muscles and in infantile onset of cardiac muscle
Pattern 1

- Proximal “limb-girdle” weakness
  - Acute/subacute – acquired
    - Inflammatory (PM/DM) – pain/rash/CTD
    - Endocrine
    - Toxic drugs
  - Chronic/congenital/painless – hereditary
    - Most dystrophies
    - Congenital
    - Mitochondrial
    - Pompe disease
    - Carnitine deficiency
Pattern 3

- Proximal arm/distal leg weakness (scapuloperoneal)
  - Facioscapulohumeral dystrophy
    - With facial weakness
  - Scapuloperoneal myopathy
  - Emery-Dreifuss humeroperoneal dystrophy
  - Lamin A/C (LGMD/B)
  - Pompe disease
  - Congenital myopathy
Clinical Features

- Slowly progressive limb-girdle weakness
- 8% of unclassified LGMD in Denmark
- Occasional scapuloperoneal syndrome
- In children, calf hypertrophy or rigid spine
- In adults, scoliosis or myalgia (50%)
- Respiratory involvement frequently and early
- FVC drop by $\geq 10\%$ once supine
- CK NL or elevated up to 15 x ULN
Work up

- EMG irritative myopathy, psp myotonia
- Muscle biopsy: vacuoles
  - PAS + cytoplasmic
  - Acid Phosphatase + autophagic
  - Vacuolization of Type I > Type II
- DBS GAA <40%
- Common mutation IVS1-13T>G
- Lumizyme FDA-approved for LOPD
- Yearly echo (5% LVH, short PR 10%)
- Yearly FVC supine & upright
The members of the AANEM Pompe Disease Study Group (in alphabetical order) are Muhammad T. Al-Lozi, MD,1 Anthony A. Amato, MD,2 Richard J. Barohn, MD,3 Edward J. Cupler, MD,4 Priya S. Kishnani, MD,5 Robert T. Leshner, MD,6 and Tahseen Mozaffar, MD.7 1Department of Neurology, Washington University School of Medicine, St. Louis, Missouri; 2Department of Neurology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts; 3Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas; 4Department of Neurology, Oregon Health and Science University, Portland, Oregon; 5Department of Pediatrics and Division of Medical Genetics, Duke University, Durham, North Carolina; 6Pediatrics and Neurology, George Washington University School of Medicine and Health Science, Washington, DC; 7Department of Neurology, University of California, Irvine, California.
Algorithm to Diagnose Late-Onset Pompe Disease

Limb-girdle syndrome

Physical examination, EMG, serum CK, and FVC seated and supine

Dyspnea secondary to ventilatory muscle weakness

Above findings suggestive of a specific alternate diagnosis

Consider alternate diagnosis

Blood-based GAA enzyme activity assay

Normal GAA enzyme activity

Reduced GAA enzyme activity

Confirm reduction of GAA enzyme activity in a second sample: lymphocytes, fibroblasts, or muscle (if available) AND/OR GAA gene sequencing

Positive Pompe disease confirmed

Negative Reassess patient and consider muscle biopsy

Above findings suggestive of Pompe disease or a nonspecific myopathy

Muscle biopsy

Findings suggestive of Pompe disease

GAA enzyme activity assay in muscle or blood

Reduced GAA enzyme activity

Normal GAA enzyme activity

Consider alternate diagnosis

Findings suggestive of an alternate diagnosis

AND/OR

GAA gene sequencing

Positive Pompe disease confirmed

Negative Reassess patient and consider muscle biopsy
A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe’s Disease

Ans T. van der Ploeg, M.D., Ph.D., Paula R. Clemens, M.D., Deyanira Corzo, M.D., Diana M. Escolar, M.D., Julaine Florence, P.T., D.P.T., Geert Jan Groeneveld, M.D., Ph.D., Serge Herson, M.D., Priya S. Kishnani, M.D., Pascal Laforet, M.D., Stephen L. Lake, Sc.D., Dale J. Lange, M.D., Robert T. Leshner, M.D., Jill E. Mayhew, P.T., Claire Morgan, M.D., M.P.H., Kenkichi Nozaki, M.D., Ph.D., Dorothy J. Park, M.D., Alan Pestronk, M.D., Barry Rosenbloom, M.D., Alison Skrinar, M.P.H., Carine I. van Capelle, M.D., Nadine A. van der Beek, M.D., Melissa Wasserstein, M.D., and Sasa A. Zivkovic, M.D., Ph.D.
LOTS Study Design

- Randomized, double-blind, placebo-controlled, 18-month trial
- 20 mg/kg every other week
  - 90 patients
  - 2:1 drug to placebo assignment
- Co-primary end points
  - 6MWT
  - FVC upright
- Secondary end points
  - QMT leg score
  - Short Form-36 physical component summary (SF-36 PCS) score
  - 6-month FVC analysis
  - 6-month walk test analysis
- All patients begin active treatment after 26th infusion prior to unblinding

LOTS Co-Primary Endpoint: 6MWT

Mean Change in Distance Walked (m)

Alglucosidase alfa

Placebo

Weeks from Baseline

P = 0.03

LOTS Co-Primary Endpoint: FVC Upright

B

Alglucosidase alfa

Placebo

Mean Change in Percent of Predicted FVC

Weeks from Baseline

P = 0.006

CONSENSUS TREATMENT RECOMMENDATIONS FOR LATE-ONSET POMPE DISEASE

Edward J. Cupler, MD1, Kenneth I. Berger, MD2, Robert T. Leshner, MD3, Gil I. Wolfe, MD4, Jay J. Han, MD5, Richard J. Barohn, MD6, John T. Kissel, MD7, and the AANEM CONSENSUS COMMITTEE ON LATE-ONSET POMPE DISEASE

1Department of Neurology, Oregon Health & Science University, Portland, Oregon, USA

2Division of Pulmonary and Critical Care Medicine, Department of Medicine and Department of Physiology and Neuroscience, New York University School of Medicine, New York, New York, USA

3Department of Neurosciences, University of California San Diego, San Diego, California, USA

4Department of Neurology, University of Texas Southwestern Medical School, Dallas, Texas, USA

5Department of Physical Medicine and Rehabilitation, University of California Davis, Sacramento, California, USA

6Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, USA

7Department of Neurology, Division of Neuromuscular Medicine, Ohio State University, Columbus, Ohio, USA
AANEM Consensus Treatment Guidelines for LOPD

- Recommendations:
  - Pre-symptomatic/no signs – no enzyme replacement Rx
    - Examine every 6 months
  - Pre-symptomatic with signs – Rx ERT
  - Symptomatic – Rx ERT
  - Symptomatic on VENT – Rx ERT but no data to support
  - For all Rx decisions – use ERT 1 year & then re-evaluate
Muscle Biopsy
More Labs

- Acid alpha-glucosidase activity was less than 2.5 and therefore not detectable (cutoff >7.45 picomoles/punch/hour)
- Repeat GAA assay at Duke 1.7
- Heterozygous intronic changes detected c.-32-13T>G is typically associated with late onset Pompe disease
Our Pompe Case series at KU

Objectives:
- Review clinical / laboratory features of LOPD
- Describe diagnostic approach
- Gain insight into response to ERT
Methods

- Retrospective chart review of LOPD cases at the University of Kansas Medical Center between 2000 and 2013
Demographics

- 17 patients with Pompe disease.
- 14 LOPD and 3 infantile Pompe
- LOPD:
  - 8 males and 6 females
  - average age of onset 24.6 years (2-51)
# Presentation

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Abbreviations: AMW axial muscle weakness, AW arm weakness, F female, LBP low back pain, LFT liver function test, LGW limb girdle weakness, LW leg weakness, M male, SOB shortness of breath.

* With scoliosis.
Presenting Clinical Features

- 8/14 limb girdle weakness
- 2/14 arm weakness
- 2/14 shortness of breath
- 1/14 myalgia
- 1/14 axial muscle weakness
Other clinical features at presentation

- 8/14 Trendelenburg gait
- 7/14 Low back pain, 3 s/p surgery
- 6/14 SOB at rest
- 4/14 Scapular winging
- 1/14 Tongue weakness
Laboratory Features

- CK range 59-1684 IU/L (mean 576):
  - 5 patients had CK <200
- FVC in 12/14, range 1.7-5.05 L:
  - abnormal in 9 patients
  - BiPAP in 4/9 patients
- EMG myotonia in 1/4
- Echo in 10/14:
  - 1 septal hypertrophy
  - 1 LVH
Muscle pathology

- N=12
  - 8/12 suspicious for Pompe
  - 4/12 nonspecific myopathy
- 5/8 vacuolar myopathy, 3 of which acid phos +ve vacuoles
- 6/8 abnormal glycogen deposition on PAS, was the only finding in 3/6
- 4 abnormal muscle GAA
DBS

- 10/14 had DBS testing:
- 8/10 blood GAA level < 40% of normal
- 2 cases GAA level ≥ 40% & confirmed by:
  - Case # 4 (48%): Muscle GAA & skin fibroblast GAA
  - Case # 7 (40%): Heterozygote for disease causing mutation
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VUS: variant of unknown significance, ND: not done
Diagnostic approach

- 8/14  Muscle Bx then DBS.
- 3/14  Muscle Bx then muscle GAA activity.
- 1/14  Fibroblast then muscle GAA activity.
- 1/14  DBS then genetic testing
- 1/14  Genetic testing then DBS
ERT

- 13 patient received ERT:
  - 11/13 reported subjective improvement on ERT or worsening on ERT holiday
  - Antibody in 6 cases: Absent or low titer in 2/6 (≤200), 1,600 to 12,800 in 4/6

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<td>14</td>
<td>1600</td>
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Conclusion of our case series

- Limb-girdle presentation is most common
- Average Diagnostic delay 8 yrs., up to 24
- Muscle pathology: most common 1st test to suspect Pompe
- Blood GAA is most common second or confirmatory test
- 50% of cases are genetically confirmed, most other are heterozygous for VUS
- Response to ERT difficult to objectively measure and independent of Ab.
Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II

Bruno Bembi · Federica Edith Pisa · Marco Confalonieri · Giovanni Ciana ·
Agata Fiumara · Rosella Parini · Mirtam Rigoldi · Arrigo Moglia · Alfredo Costa ·
Annalisa Carlucci · Cesare Danesino · Maria Gabriela Pittis · Andrea Dardis ·
Sabrina Ravaglia

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Abstract
Objectives Type II glycogenosis (GSDII) is a lysosomal storage disorder due to acid alpha-glucosidase (GAA) deficiency. Enzyme replacement therapy (ERT) with human recombinant alpha-glucosidase (rhGAA) has been demonstrated to be effective in the treatment of infantile respiratory function (vital capacity, VC; forced expiratory volume, FEV1; arterial pCO₂), and muscle enzymes were assessed every 6 months.
Results The 6MWT improved in both juvenile and adult patients ($p=0.01$, $p=0.0002$, respectively), as well as in patients with moderate to severe muscle function impair-
Long-Term Observational, Non-Randomized Study of ERT in LOPD

- N=24, 7 juvenile and 17 adult cases
- Bi-weekly infusions x 36 months.
- Clinical conditions, muscular function (6-min walking test, 6MWT; Walton scale, WS), respiratory function (VC; FEV1; arterial pCO2), and muscle enzymes assessed every 6 months
- The 6MWT improved in both juvenile and adult patients (p = 0.01, p =0.0002, respectively)
Long-Term Observational, Non-Randomized Study of ERT in LOPD

- Improvement in WS (p = 0.0003)
- VC & FEV1 remained unchanged but pCO2 decreased (p = 0.017)
- CK decreased significantly from 837 to 522 at T36 (p < 0.0001)
- Progressive clinical improvement in juvenile patients while adults reached and maintained a plateau after the first year of treatment
Impact of ERT on Survival in Adults with Pompe Disease:

- Prospective international observational study from 2002 to 2011; Erasmus MC, Rotterdam, NE
- Australia, Canada, Germany, the Netherlands, the United Kingdom, the United States & other countries
- Patients followed with annual surveys: medical h/o, current disease status, use of care & quality of life
- 283 adult patients, median age of 48 years (19-81):
  - 72% started ERT at some time during follow-up
  - 28% never received ERT

Güngör et al. Orphanet Journal of Rare Diseases 2013, 8:49
Impact of ERT on Survival in Adults with Pompe Disease:

- After adjustment for age, sex, country of residence & disease severity, ERT was positively associated with survival: hazard ratio (HR) 0.41; 95% CI, 0.19 to 0.87
- HR 0.41: at specific time point, chance of dying is 59% smaller in a patient on ERT vs. no ERT
- Median follow-up 6 years (0.04 to 9)
- Assuming adjusted HR can be interpreted as a relative risk over 4 years median & 8 years maximum follow-up (from start of ERT) & using the overall raw death rate as an estimate of the raw death rate of the treated population (16%, 46/283), eight years of ERT would result in 1 year of life gained
Conclusions

- Pompe remains to be a difficult diagnosis to make
- Pompe patients experience a long diagnostic journey
- Evidence confirms utility of ERT in Pompe in clinical practice over several year follow up:
  - improves 6 MWT distance, improves function, stabilizes FVC, & reduces CK
- Benefit may be more pronounced with earlier therapy and in juvenile cases as compared to adults
- Recent worldwide mortality data suggests a positive effect of ERT on survival
Conclusions

- Further studies are needed: survival, disability & QOL
- Standard of care should be established for all Pompe clinic visits to enable real time research in the future.
  - MMT
  - HHD
  - FVC
  - Modified Walton Scale
  - Rotterdam – 9 Item handicap Scale
  - Fatigue Severity Scale (FSS)
Thank You!