Pompe Disease: Long-Term Follow-up Clinical Guidelines

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APHL New Disorders Implementation Meeting
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Objectives

• Review diagnosis, symptoms, and treatment of Pompe disease
• Discuss clinical guidelines for follow up of patients detected by newborn screening
• Discuss challenges associated early detection of late onset Pompe disease
Pompe Disease

• Caused by lysosomal acid maltase (acid alpha-glucosidase) deficiency
  – Biallelic pathogenic variants of GAA
  – Autosomal recessive inheritance
  – Incidence of 1:15,000-1:100,000
  – More common in African Americans and Asians
• Also known as glycogen storage disease type II (GSDII)
• Classified as infantile onset (IOPD) or late onset (LOPD)
Pompe Disease

• Defective function of lysosomal acid maltase leads to accumulation of glycogen within lysosomes
  – Generalized lysosomal dysfunction
  – Release of degradative enzymes into cytosol
    • Cellular and tissue damage
    – Increased autophagy

• Primary clinical symptoms are progressive disease of cardiac and skeletal muscle
Infantile vs Late-Onset Pompe Disease

• Infantile Onset Pompe Disease (IOPD)
  – Onset of symptoms prior to 12 months old
  – Cardiomyopathy must be present to be diagnosed with “classic” IOPD
    • Signs of disease may be evident at birth or even prenatally

• Late Onset Pompe Disease
  – Onset of symptoms after 12 months old and may not be present until late adulthood
  – Cardiomyopathy may or may not be present

• Genotyping is recommended, though it cannot always distinguish IOPD from LOPD
IOPD Symptoms
LOPD Symptoms

Clinical features in Pompe disease. Atrophy of the quadriceps muscle (A), scapular winging (B), and ptosis (C) are notable clinical features in adults with Pompe disease. Photographs are printed with permission of the patients.
Treatment

• Enzyme replacement therapy (ERT)
  – Alglucosidase alfa approved by FDA in 2006
    • Standard dose: 20 mg/kg via IV infusion biweekly
    • 40 mg/kg via IV may improve clinical outcomes (Van Gelder 2016) and is increasingly used on IOPD patients
  – Immune tolerance induction ITI therapy improves efficacy

• Other specific therapies have limited impact
  – LOPD patients may benefit
    • Dietary treatment
      – Increased dietary branch chain amino acids with L-alanine supplementation
      – High calorie with reduced carbs
    • Albuterol
      – Bone marrow transplant has not been proven to be effective

• Ancillary treatments (e.g. physical therapy)
Early ERT studies

- Demonstrated prolonged life expectancy, improvement in cardiomyopathy and decreased need for assistive ventilation
- 2009 study of 18 IOPD patients treated with ERT vs historical controls:

Kaplan-Meier analyses of survival, survival free of invasive ventilation, and survival free of any ventilation. In each panel, thick solid lines show the Kaplan-Meier estimates for the treated patient group; thin solid lines show those for the historical control group, with 95% confidence intervals given by the corresponding dashed lines. Solid circles indicate right-censored observations. (A) Kaplan-Meier estimate of time from date of birth to death. Seven patients were right-censored from this analysis because they had not reached age 36 months by the end of the study, although they remained alive at that time. (B) Kaplan-Meier estimate of time from birth to invasive ventilator use or death. Four patients were right-censored from this analysis because they had not reached age 36 months by the end of the study, although they remained free of invasive ventilation that time. (C) Kaplan-Meier estimate of time from birth to any ventilator use or death. Four patients were right-censored from this analysis because they had not reached age 36 months by the end of the study, although they remained free of any ventilation that time. *Asterisk indicates that 1 patient from the historical control group remained alive at 36 months of age; this patient died at age 44 months.

ERT Outcomes

• Parini, et al 2018
  – Retrospective review of 28 Italian IOPD patients treated with ERT
    • Multi-center
    • Patients diagnosed based on clinical symptoms
      – Median age of diagnosis: 3 months
      – Median age of treatment initiation: 4 months
    • Inconsistent use of immune tolerance induction therapy (3 treated)

• Similar outcomes in studies in the UK (Broomfield 2015) and Germany (Hahn 2015)
From:
a- Overall survival (OS) and ventilation free survival (VFS) of the whole cohort of IOPD patients: at 6 years of age 58.8% (SE 9.8) and 31.8% (SE 8.6) respectively. 

b- overall cumulative incidence of cardiac normalization: at 6 years 57.8% (SE 8.6). 

c- OS of CRIM-negative (NEG) and CRIM-positive (POS). 

d- ventilation free survival of CRIM-negative and CRIM-positive. In panel c and d the relative risk (RR) of failure for CRIM-positive vs. negative is reported, together with the p-value. CRIM positives’ risk of death was 1/4 of CRIM negative patients and the risk of being ventilated was 1/5 of that of CRIM negatives.

From:
Cross-Reactive Immunologic Material (CRIM)

- **CRIM(+)**
  - Patients have residual GAA protein production
  - Generally associated with 1 or 2 missense variants in GAA
- **CRIM(-)**
  - Patients have undetectable GAA protein production
  - Generally associated with nonsense or frame shift GAA variants or with multiexon deletions

- CRIM status guides ITI therapy
  - CRIM(-) patients mount a stronger immune response to ERT, require more intense ITI, and generally have poorer response to ERT
  - A significant minority CRIM (+) patients also mount a significant immune response
  - Anti-rhGAA antibody titers are followed during ERT
- Studies of patients on combined ERT and ITI are ongoing
Example ITI Regimen

- **Alglucosidase alfa**: (20 mg/kg every other week)
- **Rituximab IV**: (375 mg/m²; if BSA < 0.5 m², 12.5 mg/kg)
- **Methotrexate SC**: (0.4 mg/kg)
- **IVIG**: (400-500 mg/kg)

Outcomes with ITI

Comparison of anti-rhGAA IgG antibody titers seen over time in CRIM-negative (CN) treated with ERT monotherapy (n=8) versus CN ERT+ITI (n=7) treated patients.

Kaplan-Meier survival curve showing comparison of ventilator-free survival CRIM-negative (CN) ERT monotherapy (n=11) versus CN ERT+ITI (n=7) treated patients.

Newborn Screening

- NBS for Pompe disease began in Missouri in 2013
- Added to HHS Recommended Uniform Screening Panel (RUSP) in 2015

[Map showing states with Yes, No, and Insufficient Data for Pompe screening]

http://www.babysfirsttest.org/newborn-screening/rusp-conditions#pompe
The Initial Evaluation of Patients After Positive Newborn Screening: Recommended Algorithms Leading to a Confirmed Diagnosis of Pompe Disease
Barbara K. Burton, David F. Kronn, Wuh-Liang Hwu, Priya S. Kishnani and on behalf of the Pompe Disease Newborn Screening Working Group

*Pediatrics* 2017;140:S14
DOI: 10.1542/peds.2016-0280D

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/140/Supplement_1/S14

Management of Confirmed Newborn-Screened Patients With Pompe Disease Across the Disease Spectrum
David F. Kronn, Debra Day-Salvatore, Wuh-Liang Hwu, Simon A. Jones, Kimitoshi Nakanura, Torayuki Okuyama, Kathryn J. Swoboda, Priya S. Kishnani and on behalf of the Pompe Disease Newborn Screening Working Group

*Pediatrics* 2017;140:S24
DOI: 10.1542/peds.2016-0280E

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/140/Supplement_1/S24
Short Term Follow Up of Positive NBS

• **Determine clinical status!**
  – Symptomatic newborns need to be evaluated emergently
  – Differentiate IOPD from LOPD

• What information does your state screening program provide? How long is turnaround time for results?

• What information is helpful in the diagnostic stage?
  – GAA activity
  – GAA genotype
  – CRIM status
  – (Creatine/creatinine)/GAA activity (Tortorelli, 2017)
First Clinical Visit

• Assess for clinical symptoms
  – Muscular disease
    • Hypotonia
    • Respiratory insufficiency/apnea
    • Poor feeding
    • Macroglossia
  – Cardiac disease
    • Cardiomegaly/hypertrophy
    • Congestive heart failure
    • Hepatomegaly
    • Rhythm disturbance

• Identify IOPD patients in need of treatment
First Clinical Visit

• Labs
  – Creatine Kinase (CK) level
    • Elevated in IOPD
    • Mildly elevated or normal in LOPD
  – Urine hexose tetrasaccharide (Hex4)
    • Elevated in IOPD and may precede signs of muscle weakness
    • Normal in LOPD
  – Others as needed

• Studies
  – Chest X ray
  – EKG
  – Echocardiogram

• Determine CRIM status
  – Genotype is predictive in majority of cases
  – Fibroblast and blood based assays are available through a limited number of labs/research studies

• Determine whether to begin ERT and which concurrent ITI regimen is needed

• Coordination of care
• Genetic counseling and evaluation of family members
### Long Term Follow-up of IOPD

**Table 3: Classic Infantile-Onset Pompe Disease (CRIM-Negative and CRIM-Positive): Recommended Follow-up Schedule and Assessments for Patients**

<table>
<thead>
<tr>
<th>Assessment Time Point and Frequency</th>
<th>Initial Newborn Referral</th>
<th>2–4 wk of Age</th>
<th>Monthly to 4 mo of Age</th>
<th>Every 2 mo (4–12 mo of Age)</th>
<th>Every 3–6 mo (≥12 mo of Age)</th>
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A change in clinical status may indicate a need for additional intervention. For patients who are on ITI, laboratory assessments for safety of the ITI regimen, including ALT, AST, and complete blood count, should be done. BAER, brainstem auditory-evoked response; CK-MB, CK myocardial band; ECG, electrocardiogram; EF, ejection fraction; HC, head circumference; HT, height; Hx, history; LVM, left ventricular mass index; SF, shortening fraction; WPW, Wolff-Parkinson-White. —, not applicable.

<sup>a</sup> As clinically indicated.

<sup>b</sup> Varies with patient's genotype.

<sup>c</sup> Denver: Bailey; TIMP; AIMS, Gross Motor Function Measure-88; CHOP INTEND. Videotaping can be done and used to assess patients.

<sup>d</sup> Rise in antibodies of >25:800 may indicate a need for immune modulation.

<sup>e</sup> Antibody titers levels indicating a need for immune modulation are based on antibody testing done by Sandofi Genzyme, Cambridge, MA.

<sup>f</sup> Should be measured before treatment initiation at initial evaluation or at 2–4 wk.

Detection of LOPD
“Patients in Waiting”

• Pros
  – Detection and treatment of IOPD
  – Avoidance of diagnostic odyssey and associated costs
  – Early treatment of LOPD
  – Reproductive counselling
  – Advancing medical knowledge

• Cons
  – Medicalization or stigmatization of LOPD children
  – Psychological burden to patient and families
    • Uncertain long term course, including need/risk of treatment
    • Loss of autonomy
    • Insurance discrimination
    • “Research” subjects
  – Difficulty maintaining follow up
  – Increased costs associated with surveillance
LOPD Follow-up
Asymptomatic LOPD follow up

### TABLE 5 Asymptomatic LOPD: Recommended Follow-up Schedule of Assessments

<table>
<thead>
<tr>
<th>Assessment Time Point and Frequency</th>
<th>Initial Newborn Referral</th>
<th>1 mo of Age</th>
<th>3 mo of Age</th>
<th>6 mo of Age</th>
<th>9 mo of Age</th>
<th>12 mo of Age</th>
<th>Every 3–12 mo&lt;sup&gt;b&lt;/sup&gt; (1–3 y of Age)</th>
<th>Annually&lt;sup&gt;c&lt;/sup&gt; (After 3 y of Age)</th>
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Any change in status may indicate a need for additional evaluation or treatment. BAER, brainstem auditory evoked response; ECG, electrocardiogram; HC, head circumference; Ht, height; Hx, history; —, not applicable.

<sup>a</sup> Varies with patient’s genotype.

<sup>b</sup> As clinically indicated.

<sup>c</sup> For milder genotypes.

<sup>d</sup> If CK levels are elevated at these assessment time points.

<sup>e</sup> Denver, TIMP, CHOP INTEND.

c.-32-13T>G Variant

• Most common pathogenic allele in Caucasians
  – Found on at least one allele in up to 90% of cases
  – Associated with adult onset disease in compound heterozygotes and mild/no disease in homozygous individuals

• Recent study of infants detected by NBS (Rairikar, 2018)
  – Partly funded by manufacturer of alglucosidase alfa
  – 7 consecutive self-referred patients after positive NBS
    • 3 patients compound heterozygous with c.-32-13T>G
    • 4 patients with homozygous c.-32-13T>G
  – 7/7 demonstrated some degree of motor involvement by 6 months
    • All compound hets had hypotonia and delayed motor milestones
      – Started on ERT and demonstrated improvement
    • Homozygotes with more subtle symptoms were not started on ERT
Clinical LOPD Anecdotes

4/5 of Pompe diagnoses in East TN since July 2017 have been LOPD

Patient 1
- 1 Pathogenic variant, one VUS
- Very resistant to initial evaluation after positive screen
- Refuses to follow up with genetics, though will follow with cardiology

Patient 2
- c.-32-13T>G compound heterozygote
- Mildly elevated CK, normal cardiac evaluation, normal urine Hex4
- Declined sibling testing, did not show up for audiology appointment (x2)

Patient 3
- c.-32-13T>G homozygote
- Difficulty getting approval for cardiac studies on “asymptomatic” patient

Patient 4
- c.-32-13T>G homozygote
- Teenage first-time mother with much anxiety though genotype is reassuring
Family Impact of NBS

• Pruniski, et al, 2018
  – Examined impact of diagnosis of IOPD or LOPD by NBS on families via phone interviews
  – Families recruited patient support groups, LSD clinics (9 enrolled)
    • $25 gift certificate incentive
    • Eligibility criteria were diagnosis by NBS and English speaking
    • 3 IOPD, 6 LOPD
  – Selection bias
    • 9/9 were Caucasian
    • 9/9 were mothers
    • 4/9 had household income >$100,000/year
    • 6/9 had graduate degrees
Advice to Healthcare Providers

• Faster diagnostic process
• Find better ways to communicate results
  – Genetic counselors were helpful
• Support for families
  – Uncertainty, fear and anxiety reported by all families
  – IOPD vs LOPD groups
• Education for parents and providers
  – Provide patient friendly information
  – “…I asked him even just how to spell it so I could google it…and he (the physician) didn’t know how to spell it; he wasn’t sure.”
References


