What is Your Diagnosis?

CHIEF COMPLAINT
3½ month-old Caucasian female admitted to a local hospital with the following: failure to thrive, wheezing. At admission patient was noted to have an S3 gallop and hepatomegaly. Chest X-ray showed an enlarged heart and the patient was then transferred to Egleston hospital for a cardiac evaluation. One week prior to admission the patient began wheezing and was noted to have decreased PO intake. Patient’s growth parameters at this admission were noted to be: weight in the 10th percentile, height in the 50-75th percentile and head circumference in the 50th percentile. Also noted was the patient had marked hypotonia, positive head lag, and frog leg position when on back.

PAST MEDICAL HISTORY
Patient was the product of a 39 week gestation, scheduled C-section secondary to previous C-section and history of herpes. Pregnancy was uncomplicated. At birth, weight was in the 90th percentile, height was in the 75th percentile, and head circumference was in the 75-90th percentile. The patient had been seen in the past by her pediatrician for wheezing.

PHYSICAL EXAM
You find the following: a protruding tongue, wheezing, enlarged liver that is palpable 3½ cm below the right costal margin. Electrocardiogram reveals biventricular hypertrophy, PR interval at 80 milliseconds. Echocardiogram shows massive thickening of ventricular walls and septum, small patent ductus arteriosus.

FAMILY HISTORY
See pedigree. Parents do not have known relatives in common.

1. Which of the following tests are likely to lead to the diagnosis?
   A. Plasma amino acids
   B. Urine organic acids
   C. CK and acid maltase activity
   D. Acyl carnitine profile
   E. Lysosomal enzyme screen

2. What is the most likely diagnosis for your patient?
   A. Limb-girdle muscular dystrophy
   B. Pompe disease
   C. Duchenne muscular dystrophy
   D. Polymyositis
   E. Spinal muscular atrophy type I (Werdnig-Hoffman)

3. What is the recurrence risk for this disorder?
   A. 1% or less
   B. 25%
   C. 50%
   D. 50% if female
**FINAL DIAGNOSIS**
The enzyme assay results confirmed the diagnosis of alpha glucosidase deficiency, glycogen storage disease Type II (Acid Maltase Deficiency or Pompe disease). (question 2)

**FOLLOW-UP**
Your patient returned to genetics clinic at 6 months of age. She had been followed by her pediatrician and cardiologist and had not required digitalization. Developmentally patient was at about a 3 month level. Patient followed 90 degrees, reached out, cooed, and smiled responsively. Patient was unable to lift head, follow 180 degrees, make word sounds, bear weight or sit. She was very hypotonic. Weight was at less than the 5th percentile, height at the 5th percentile and head circumference at the 25th percentile. Liver was enlarged at about 3 cm below the right costal margin. You note that patient has head lag, but can hold head in midline if supported, no reflexes. You counsel the parents regarding inheritance, prenatal testing, recurrence risk and poor prognosis. You give the patient’s parents information on a local support group and hospice. The patient eventually died at 9 months of age due to cardiorespiratory failure.

**ABOUT POMPE DISEASE**
First described in 1932 by Dutch physician J.C. Pompe, Pompe disease is a rare and often fatal metabolic muscle disease caused by an inherited deficiency of the enzyme acid alpha-glucosidase (GAA), which is responsible for breaking down excess glycogen in cellular compartments known as lysosomes. Pompe disease ranges from a rapidly fatal infantile-onset form with severe cardiac and respiratory involvement to a more slowly progressive late-onset form primarily affecting skeletal muscle.

**Infantile-onset Pompe disease** typically presents rapidly with initial observations of profound hypotonia, muscle weakness, and a “floppy baby” appearance. The hallmark sign is marked cardiomegaly, although feeding difficulties and respiratory problems may manifest at early stages as well. Death from cardiorespiratory failure usually occurs by 12 months of age.

**Late-onset Pompe disease** can present anytime during early childhood up until adulthood with progressive muscle weakness and / or respiratory insufficiency. The disease course for late-onset Pompe disease varies widely, making morbidity and life expectancy difficult to predict. Death usually results from respiratory failure.
DIAGNOSIS (question 1)
Enzyme activity testing is the definitive diagnosis for Pompe disease. This is best performed using cultured skin fibroblasts. (Lysosomal enzyme screens do not usually include Pompe, and are not standard of care for testing at this time). If the patient’s acid alpha-glucosidase (GAA) is decreased or nonexistent, a conclusive diagnosis can be made. Most infants with Pompe have less than 1% of normal enzyme activity, juveniles less than 10%, and adults less than 40%. Patients may also demonstrate elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and in some instances, a chest X-ray showing the presence of cardiomegaly provides the first indication of Pompe disease. Ninety percent of patients with Pompe disease have elevated CK levels, which focuses the diagnosis inquiry on a muscle disorder.

Infantile-Onset
- Progressive muscle weakness and profound hypotonia (96%)
- Cardiomegaly (95%) and/or cardiomyopathy
- Hepatomegaly (82%)
- Macroglossia (62%)
- Delayed developmental motor milestones
- Respiratory insufficiency and/or frequent infections
- Feeding difficulties and/or failure to thrive

Late-Onset
- Progressive muscle weakness (especially in the trunk and lower limbs)
- Respiratory insufficiency
- Sleep apnea / fatigue
- Gait abnormality
- Delayed motor milestones (children)

GENETICS & DISEASE FREQUENCY
- Autosomal Recessive Inheritance: with each pregnancy, when parents are carriers for a disease-causing mutation in the GAA gene, there is a 1 in 4 or 25% chance of having a child affected with Pompe disease. (question 3)
- Predicted live birth incidence of 1:40,000 (of all types)
- Pan-ethnic with some variance:
  - Estimated African-American incidence: 1:14,000 (infantile-onset)
- Estimated prevalence of several thousand worldwide

PRENATAL DIAGNOSIS
Prenatal diagnosis for Pompe disease is available via chorionic villus sampling (CVS) or amniocentesis.

MANAGEMENT & TREATMENT
Supportive therapy for Pompe disease is used to manage symptoms and minimize complications. The Emory Lysosomal Storage Disease Center (404-727-3930) will be participating in worldwide clinical trials to determine the safety and effectiveness of enzyme replacement therapy for Pompe. Studies examining the efficacy of bone marrow transplantation, and the feasibility of gene therapy for Pompe disease, are also being conducted.

ADDITIONAL RESOURCES
Acid Maltase Deficiency Association
www.amda-pompe.org
Genzyme Corporation
www.genzyme.com
Pompe Community
www.pompe.com
Muscular Dystrophy Association
www.mdausa.org
Genzyme medical Information
1(800)-745-4447
If you have additional questions about Pompe disease, please call Emory Genetics at 1-800-366-1502 or (404) 297-1500 and ask for the Genetic Counselor On-Call, or fill out the information below, and fax this page to: FAX (404) 297-1517.

Thank you.

Name_______________________________________________________________________
Address_____________________________________________________________________
Phone_________________________________FAX__________________________________

I am interested in:

_____Having a question answered about one of my patients.

_____Referring a patient to the Lysosomal Storage Disease Center.

_____Receiving this newsletter fax. Please add me beginning next month.
   (Name, address, phone, and fax# above must be completely filled out.)

_____Other:________________________________________________________________

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