What is Your Diagnosis?

CHIEF COMPLAINT
An eight month old Hispanic male is admitted to a local hospital with the following complaints: failure to thrive, recurrent ear infections, and pneumonia. At admission, the baby is noted to have a tower-like skull, flat face, prominent bulging eyes, limited range of motion in hips and neck, and developmental delays. A complete skeletal survey finds that the baby has short thick ribs, short thick femora and humeri, bullet-shaped phalanges, and beaking of the vertebrae. A brain MRI was normal. Prior to his admission, the patient had chronic upper respiratory infections. The patient’s growth parameters at admission were noted to be: weight and height less than 5% of normal and a head circumference in the 50% percentile.

PAST MEDICAL HISTORY
Patient was the product of a 39 week gestation, normal vaginal delivery. Pregnancy was uncomplicated. The baby was noted to have congenital dislocation of the hips at birth. At birth, weight, height, and head circumference were in the 50% percentile. The patient is a frequent visitor to his pediatrician with recurrent upper respiratory tract and ear infections.

PHYSICAL EXAM
You find the following: Enlarged liver that is palpable 2 cm below the right costal margin, small nose with flat nasal bridge and upturned nares, large tongue, enlarged gums, coarse facial features, a murmur, clear corneas, and a small lumbar gibbus deformity

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

Test yourself: answer these questions before reading the answers on page 2.

1. Which of the following tests will most likely lead to a clear diagnosis?
   A. Comprehensive Lysosomal enzyme analysis
   B. Urinary glycosaminoglycans (GAGs)
   C. Plasma amino acids
   D. Urinary organic acids

2. What is the most likely diagnosis for your patient?
   A. Pompe disease
   B. Hurler syndrome (Mucopolysaccharidosis Type I)
   C. Saethre-Chotzen
   D. I-cell disease (Mucolipidosis Type II)
   E. Gaucher disease, type III

3. What is the recurrence risk for this disorder?
   A. 1% or less
   B. 25%
   C. 50%
   D. 100%
FINAL DIAGNOSIS
The combination of physical features and the lysosomal enzyme assay results confirmed the diagnosis of I-cell disease, mucolipidosis Type II. (question 2) At the time of the exam, you strongly considered a diagnosis of Hurler syndrome (Mucopolysaccharidosis Type I) or Hunter syndrome (Mucopolysaccharidosis Type II). You ruled out Hurler syndrome based on the clear corneas and multiple elevated lysosomal enzymes. You ruled out Hunter syndrome based on the multiple elevated lysosomal enzymes.

FOLLOW-UP
Your patient recovered from his pneumonia and was referred to pediatric pulmonology, pediatric orthopedics, pediatric ENT, pediatric cardiology, and the medical genetic department’s lysosomal storage disease clinic. You counsel the parents regarding inheritance, prenatal testing, recurrence risk, and poor prognosis. You give the patient’s parents information on the appropriate support groups. You discussed the option of bone marrow transplant with the parents, but they declined based on the morbidity and mortality of the procedure. You treat the patient’s progressive failure to thrive with nutritional supplementation and promptly treat his recurrent respiratory infections with antibiotics.

At one year of age, the patient smiles, follows and grasps objects, but is unable support weight on his legs. The patient’s gibbus continues to worsen and his hands stiffen into a “claw-hand deformity”. The patient develops joint contractures and an inguinal hernia. The patient continues to have recurrent upper respiratory and ear infections including aspiration pneumonia. Although there is no treatment that is available at this time, you keep in touch with your local lysosomal storage disease center to learn about research and information on I-cell disease.

ABOUT I-CELL DISEASE
First described in 1967 by Leroy and DeMars, I-cell is a fatal lysosomal storage disorder caused by mutations in the GNPTA gene that lead to a deficiency in the enzyme UDP-N-acetylglucoseamine-1-phosphotransferase. Deficiency of UDP-N-acetylglucoseamine-1-phosphotransferase prevents the addition of a recognition marker or “signal” necessary for the transportation of lysosomal enzymes into the lysosome. Since they are missing the transportation “signal”, the lysosomal enzymes cannot enter into the lysosome to break down specific fatty substances (mucolipids) and complex carbohydrates (mucopolysaccharides). Some lysosomal enzymes are able to enter the lysosome through a different pathway that doesn’t require the recognition marker added by the missing “signal”, but the remaining enzymes stay outside of the lysosome.

I-cell disease typically presents in the first six months of life with developmental delays, failure to thrive, and chronic upper respiratory infections. Some physical signs, such as hip dislocations, inguinal hernias, hepatomegaly, joint limitations, and skin changes may be present at birth. Coarse facial features and skeletal abnormalities become more conspicuous over the first year. Some patients will exhibit corneal clouding, but others will not. Many individuals affected by I-cell disease will develop an enlarged heart.
and cardiomyopathy as the disease progresses. Although the progress of the disease varies from individual to individual, affected children typically do not live past the first decade of life. Most individuals affected by I-cell disease die in the first 3-4 years of life.

**DIAGNOSIS**

Lysosomal enzyme activity testing is the definitive diagnostic test for I-cell disease. Various lysosomal enzyme activities should be measured in both serum and cultured skin fibroblasts. In I-cell disease, the activities of beta-hexosaminidase, iduronate sulfatase, and arylsulfatase A are deficient in cultured skin fibroblasts but are 10-20 times normal in serum. Assays for lysosomal enzymes in leukocytes are not reliable because of mannose-6-phosphate–independent targeting pathways. N-acetylglucosaminyl-1-phosphotransferase activity can be measured in white blood cells or in cultured fibroblasts, but is not part of the standard lysosomal enzyme panel and needs to be ordered specifically from a specialty lab. Although urinary glycosaminoglycans (GAGs) will be negative in ML-II, they may rule out other lysosomal storage disease conditions such as Hurler syndrome (Mucopolysaccharidosis Type I) in a comprehensive work-up.

**Key Signs and Symptoms of I-cell disease**

- Failure to thrive
- Developmental delays
- Hypotonia
- Coarse facial features
- Gum overgrowth (gingival hyperplasia)
- Enlarged tongue (Macroglossia)
- Frequent upper respiratory tract infections
- Inguinal and Umbilical hernias
- Enlarged liver (hepatomegaly)
- Murmur of aortic insufficiency
- Widening of ribs
- Gibbus and kyphoscoliosis
- Hip dislocation
- Bullet shaped phalanges
- Claw hand deformity
- Joint limitation/contractures

**GENETICS & DISEASE FREQUENCY:**

- **Autosomal recessive inheritance:** When parents are carriers for an I-cell causing mutation in the gene coding N-acetylglucosaminyl-1-phosphotransferase, with each pregnancy there is a 1 in 4 or 25% chance of having a child affected with I-cell disease. *(question 3)*

- One study found an estimated frequency of I-cell disease of approximately 1 in 640,000 live births.

- Pan-ethnic (appears in every racial group).

**PRENATAL DIAGNOSIS**

Prenatal diagnosis for I-cell disease is available via chorionic villus sampling (CVS) or amniocentesis.

**MANAGEMENT & TREATMENT**

Treatment for I-cell disease is very limited. In the literature there is one report of a successful bone marrow transplant (BMT) stopping the progress of the disease; however, damage that is already done cannot be reversed through BMT.

In the vast majority of cases, supportive therapy for I-cell disease is used to manage symptoms and minimize complications. Common therapies include: physical therapy, nutritional supplementation, and prompt treatment of recurrent respiratory infections with antibiotics. In addition, children with I-cell disease have an increased risk for complications during general anesthesia due to the accumulation of the storage produces in the nasal passages, tonsils, adenoids, tongue, and larynx. The increased anesthesia risks need to be discussed with the parents, anesthesiologists, and members of the medical team well before any surgery or anesthesia is performed. One study is currently looking at increased quality of life with the use of bisphosphonates to decrease bone pain. No therapies which address the underlying genetic defect are available or in clinical trials at this time. Referral for palliative care and hospice services are indicated during the terminal phases of the disorder.

The Emory Lysosomal Storage Disease Center (404-778-8565) follows research on I-cell disease closely and members of the team are available to discuss current research as it emerges. Comprehensive lysosomal enzyme analysis and urinary glycosaminoglycan testing are available through Emory Genetics Laboratory (www.genetics.emory.edu).
If you have additional questions about I-cell disease, please call the Emory Lysosomal Storage Disease Center at 1-800-200-1524 or (404) 778-8565, or fill out the information below, and fax this page to: FAX (404) 778-8559.

Thank you.

Name_______________________________________________________________________

Address_____________________________________________________________________

Phone_________________________________FAX__________________________________

I am interested in:

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

_____Removing my fax number from the newsletter fax.

_____Other:________________________________________________________________

PLEASE NOTE: In accordance with the Federal Communications Commission, this newsletter fax is for educational purposes only. Recipients may request removal by filling out the above information and faxing this page to: (404) 778-8559.