What is Your Diagnosis?

Chief Complaint - 8 y.o. Caucasian female presents with the following history:
• History of recurrent ear infections
• Umbilical hernia repair at age 5
• Adenotonsillectomy at age 7
• Chronic mouth breathing and snoring
• Corneal clouding
• Developmentally normal

On Physical Exam, you note:
• Restricted shoulder extension
• Hepatosplenomegaly

Family History - See pedigree. Parents do not have known relatives in common.

After reviewing this information, answer the questions below, before reading the answer on page 2.

Take the Genetic Challenge:

1. Your diagnosis for the proband is:
   A) Multiple sulfatase deficiency
   B) Mucopolysaccharidosis, type I
   C) Mucopolysaccharidosis, type VI (Maroteaux-Lamy)
   D) Gaucher Disease, Type I
   E) Mucolipidosis III
   F) I-cell Disease

2. Which of the following would you order on your patient:
   A) DNA Test
   B) Urinary GAGs
   C) Urine Organic Acids

3. What is the most likely inheritance pattern of the disorder in your patient’s family?
   A) Autosomal Recessive
   B) Autosomal Dominant (one of the parents has gonadal mosaicism)
   C) X-linked Recessive
   D) Mitochondrial

continued...
If you answered B) for questions 1 &2, and A) for question 3, congratulations! You have mastered this month's Genetic Challenge!

Lab Tests Ordered:
- MPS screen showed abnormal glycosaminoglycans (GAGs), 102.7 mg GAG/gm creatinine (normal is 10.3 - 75.3). GAGs identified dermatan sulfate, chondroitin 4-sulfate, chondroitin-6 sulfate.
- Enzyme assay for alpha-L-iduronidase revealed an enzyme level in leukocytes of 0.337 nmol/hr/mg protein (compared to control values of 5.21 and 6.09).

Diagnosis/Impression:
Mucopolysaccharidosis type I (Hurler-Scheie) intermediate form. Sister most likely also affected.

Plan:
1. Treat with Aldurazyme® enzyme replacement therapy* at .58 mg/kg/week.
2. Obtain baseline studies: echocardiogram, PT assessment to include range of motion, developmental assessment, pulmonary function tests, skeletal survey, MRI/CT for liver and spleen volumes, ophthalmologic exam, hearing exam, MRI of brain if head size is large.
3. Monitor pulmonary function, range of motion, cardiac function, corneal clouding, hearing, development, head size, and organ volumes.
4. Intercede with PT, OT, and/or speech therapy if needed.

*On April 30, 2003, the FDA approved the first treatment for patients with MPS I disease (http://www.fda.gov/cber/products/larobio043003.html). “This disease results from the absence or malfunctioning of an enzyme that breaks down molecules called glycosaminoglycans (GAG) in the cells. The build up of GAG in the cells of patients with MPS I results in progressive cellular damage that affects appearance, physical abilities, organ functions and, in some cases, mental development. The new biotechnology product, Aldurazyme (laronidase), is a version of the human form of the deficient enzyme. This new biotechnology product helps prevent the buildup of GAG in the cells and has been shown to improve lung function and exercise ability. Aldurazyme’s approval is for patients with Hurler and Hurler-Scheie forms of MPS I as well as patients with the Scheie form with moderate to severe symptoms.”

About Mucopolysaccharidosis type I (MPS I)
MPS I is an autosomal recessive lysosomal storage disease that encompasses three syndromes: Hurler, Hurler-Scheie, and Scheie syndromes, better described as severe, intermediate, and mild MPS I. All types of MPS I are caused by a deficiency in an active enzyme, alpha-L-iduronidase, which results in a buildup of carbohydrate materials called glycosaminoglycans (GAGs) in all tissues of the body. This buildup of stored material leads to cell, tissue, and organ dysfunction. The debilitating effects of MPS I can lead to early death - often before the age of ten in the severe phenotype. Symptoms can include enlargement of the liver and spleen, joint pain and immobility, skeletal deformity, vision impairment, stunted growth, hearing loss, obstruction of airways, severe headaches and cardiomyopathy.

Clinical Overview
The three clinical phenotypes of MPS I cannot be distinguished biochemically, and the clinical criteria to delineate between the three has not been determined, and is best described as severe, intermediate, or mild. It is estimated that 80% of patients fall in the severe end. However, patients with mild or intermediate disease make up a larger proportion of patients due to increased longevity.
Severe MPS I (Hurler syndrome)
Severe MPS I patients are normal at birth, with a diagnosis between 9 and 18 months of age. The scope of this newsletter does not permit an adequate explanation of the severe MPS I phenotype. They have severe involvement of multiple organs and death usually occurs in the first 10 years of life.

Intermediate MPS I (Hurler-Scheie Syndrome) and Mild MPS I (Scheie Syndrome)
Clear clinical criteria do not exist to delineate between intermediate and mild MPS I. Usually the intermediate form onsets between three and eight years of age, with survival into adulthood. Intellect is variable but can be normal, regardless of other symptoms. There is progressive somatic involvement with intermediate MPS I including dysostosis multiplex, arthropathy, corneal clouding, joint stiffness, deafness, variable growth retardation, and valvular heart disease.

Mild MPS I patients are usually diagnosed after 15 years of age and tend to have normal intellect, stature, and life-span. The major clinical problems are arthropathy, carpal tunnel syndrome, aortic valve disease, slight organomegaly, corneal clouding, glaucoma, retinal degeneration, and mild facial coarseness.

Cervical cord compression and spondylolisthesis of the lower spine resulting in spinal cord compression can occur in both the mild and intermediate forms of MPS I. In addition, both have facial features that are less coarse than the severe form. Skeletal and joint problems are the most significant cause of disability in these two forms.

Diagnosis:
The diagnosis of MPS I is demonstrated by deficient activity of the lysosomal enzyme alpha-L-iduronidase in peripheral blood leukocytes, cultured fibroblasts, or plasma. Alpha-L-iduronidase is a glycosidase that removes the non-reducing terminal alpha-L-iduronide residues during the lysosomal degradation of the glycosaminoglycans heparan sulphate and dermatan sulphate. Testing for urinary GAGs (qualitatively or quantitatively) is a useful preliminary test; if abnormal, an MPS disorder is likely.

The iduronidase-A (IDUA) gene on chromosome 4 is mutated in patients with MPS I disease; genotype-phenotype correlations exist. Clinical testing is available, and both mutations are detected in >95% of patients. Carrier testing on parents and siblings of an affected individual can be done when both mutations in the proband have been identified. Prenatal diagnosis is also available.

Pathophysiology:
MPS I disease is caused by a defect in the gene coding for the lysosomal enzyme alpha-L-iduronidase. As a result of this defect, the cells of people with MPS I are either unable to produce the enzyme or produce it in low amounts. This results in an inability of the lysosome to act in the stepwise degradation of the glycosaminoglycans dermatan sulfate and heparan sulfate. These glycosaminoglycans are important constituents of the extra cellular matrix, joint fluid, and connective tissue throughout the body. In MPS I disease, they progressively accumulate in the lysosome. Ultimately, the accumulation causes cell, tissue, and organ dysfunction. MPS I is considered to be the prototypical lysosomal storage disorder with progressive multi-systemic disease and presenting features that vary depending on where a patient is on the disease continuum.

Frequency:
The estimated prevalence of MPS I disease is 1 in 100,000 for the severe form and 1 in 500,000 for the mild form. However, the true prevalence of the disease will not be known until newborn screening is possible. The disease is present in all ethnic, racial, and demographic groups. Approximately 2,000-3,000 patients in the world have been diagnosed with MPS I. As with other lysosomal storage diseases, there are believed to be additional undiagnosed patients.
Treatment:
Prior to enzyme replacement therapy, the primary management of MPS I was supportive care. In severe cases, bone marrow transplantation may be considered. While there is no cure for MPS I disease at this time, Aldurazyme® enzyme replacement therapy (laronidase) is available. A MPS I Registry has been established for patients to better understand the variability and progression of MPS I disease and to monitor the long-term treatment effects of Aldurazyme® (www.mps1registry.com).

Conference: A MPS I disease management training program will be held on August 9, 2003 at the Emory Inn & Conference Center in Atlanta, Georgia. Call (404) 727-3930 for more information.

References:
- www.genetests.org (GeneReviews)
- www.aldurazyme.com
- www.mpssociety.org

If you have additional questions about MPS I disease or other lysosomal storage disorders, call the Emory Lysosomal Storage Disease Center at (404) 727-3930, or fill out the information below, and fax this page to: FAX (404) 297-1517.

Thank you.

Name________________________________________________________________
Address______________________________________________________________
Phone___________________________E-mail_______________________________

I am interested in:

_____ Obtaining additional written information about MPS I.
_____ Sending a sample to Emory Genetics Laboratory for MPS I testing.
_____ Having a question answered about one of my patients.
_____ Learning more about enzyme replacement therapy for MPS I disease.
_____ I would like to receive this newsletter fax. Please add me beginning next month.
_____ Other:__________________________________________________________________________

"Take the Genetic Challenge!", now online at: www.genetics.emory.edu
(click on "I am a Physician")