What is Your Diagnosis?

CHIEF COMPLAINT
A 12 month old Caucasian male presents with the following history:
- Developmental delay
- Unusual facial features
- Gibbus deformity
- Skeletal changes prompting concern of a skeletal dysplasia
- Failure to thrive

PAST MEDICAL HISTORY
The patient is the product of an uneventful first pregnancy. He had an inguinal hernia repaired at 5 months of age. His diet consists of soy formula due to lactose intolerance. He has had no major illnesses and does not take any medications. He was able to support himself on his forearms in prone position at 3 months of age, and was rolling over at 4 months, but was not able to sit unsupported until 10 months. He is not yet crawling, cruising, or walking.

PHYSICAL EXAM
You note that the patient has coarse facial features, corneal clouding, and mild macroglossia. The patient has hepatosplenomegaly and a thoracolumbar gibbus. His fingers are short with unilateral clawing of the 3rd digit.

ADDITIONAL ASSESSMENTS
Based on the history and physical exam, you suspect that the patient has a lysosomal storage disorder. Therefore, you order a skeletal radiologic survey that identifies features consistent with dysostosis multiplex.

FAMILY HISTORY
See pedigree. Patient’s parents do not have any known relatives in common. The family shares with you that they are planning to conceive a second pregnancy within the next year.
If you answered 1) D, 2) C, 3) B, and 4) C&D for each question, congratulations! You have mastered this month's Genetic Challenge!

FINAL DIAGNOSIS
Mucopolysaccharidosis type I (MPS I) [question 2]. The urine MPS screen revealed abnormal glycosaminoglycans (GAGs) of 196.4 mg GAG/gm creatinine (normal is 2.9 - 80.5). Qualitative GAGs identified included dermatan sulfate, chondroitin 4-sulfate, and chondroitin-6 sulfate. The enzyme assay for alpha-L-iduronidase revealed an enzyme level in leukocytes of 0 pmol/hr/mg protein (control range of 100-350 pmol/min/mg protein).

FOLLOW UP
After a quick search on the internet, you find that there is a lysosomal storage disease center in your area that can assist you with coordination of patient care, genetic counseling, discussion of treatment options, and participation in research trials. You provide the family with information about treatment options for their son, including enzyme replacement therapy and hematopoietic stem cell transplantation. You also make referrals to obtain baseline studies including echocardiogram, PT assessment to assess range of motion, developmental assessment, pulmonary function tests, MRI/CT for liver and spleen volumes, hearing exam, and brain/spine MRI.

ABOUT MUCOPOLYSACCHARIDOSIS TYPE I
MPS I is a progressive, autosomal recessive genetic disorder resulting from a defect in the gene for the lysosomal enzyme α-L-iduronidase. The genetic defect leads to a partial or complete deficiency of α-L-iduronidase and, subsequently, progressive accumulation of the glycosaminoglycans (GAGs), dermatan sulfate and heparan sulfate. GAGs are complex polysaccharides that are an important component of the extracellular matrix and connective tissues throughout the body. Deficiency of this enzyme leads to accumulation of GAGs in the lysosome, ultimately resulting in cell, tissue and organ dysfunction.

MPS I occurs in severe, intermediate, and milder forms that cover a broad spectrum of symptoms and disease progression. MPS I is now considered a spectrum of disease, though in the past, it was divided into three subtypes based on disease severity: “Hurler” for severe MPS I, “Hurler-Scheie” for intermediate MPS I, and “Scheie” for mild MPS I. The heterogeneity of MPS I disease demonstrates a wide range of clinical involvement marked by umbilical and inguinal hernias, skeletal abnormalities, recurrent and persistent upper respiratory tract infections, coarse facial features, arthropathy, hydrocephalus, spinal root and peripheral nerve entrapment, obstructive airway disease, sleep apnea, hearing loss, massive hepatosplenomegaly, corneal clouding, glaucoma, retinal degeneration, optic atrophy, cardiac valvular and ischemic myocardial damage. As MPS I progresses, complications become debilitating and often life threatening.

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. However, the amount of residual enzyme does not predict disease severity. Testing for urinary GAGs (qualitatively or quantitatively) is a useful preliminary test; if abnormal, a MPS disorder is likely [question 1].

MOLECULAR TESTING
MPS I is caused by mutations in the iduronidase-A (IDUA) gene on chromosome 4. For some mutations, genotype-phenotype correlations do...
Gene sequencing for MPS I is clinically available through Emory Genetics Laboratory and both mutations are detected in >95% of patients. Once the underlying gene mutation(s) has been identified by sequencing, family members can have carrier testing and couples can have prenatal testing, targeted for the specific gene mutation(s) [question 4]. For couples with a family history of MPS I but no living affected relatives available for testing, sequencing is available for the couple to clarify genetic counseling concerning their carrier risk. Couples who have had an affected child with MPS I are obligate carriers and have a 1 in 4 or 25% risk for recurrence in future pregnancies [question 3].

TREATMENT OPTIONS
There is no cure for MPS I. Currently, a hematopoietic stem cell transplant (HSCT) from bone marrow or umbilical cord blood is the only proven therapy that can stabilize neurocognitive development and improve survival in patients with MPS I. Bone marrow transplant is most advantageous when performed on a patient with minimal symptoms of MPS I (typically before 2 years of age). HSCT has its own associated risks for complications, including developing graft versus host disease. The risk of severe complications and death varies depending upon several factors, including pulmonary function and whether there is a related versus unrelated donor.

Another available treatment option for MPS I is enzyme replacement therapy with Aldurazyme®. This drug is the only enzyme replacement therapy available that treats the underlying cause of MPS I. Aldurazyme has been shown to improve pulmonary function, endurance and functional capacity as well as decrease glycosaminoglycans (GAG, the accumulated substrate), and reduce hepatomegaly in patients with this disorder. The therapy has not been evaluated for effects on the central nervous system manifestations of this disease. Aldurazyme® is administered intravenously at a dose of 0.58 mg/kg, typically on an outpatient basis once per week.

REFERENCES & ADDITIONAL INFORMATION:
Emory Genetics Laboratory
http://www.genetics.emory.edu/testing/test.php?test_id=138

Gene Reviews
http://www.genetests.org/query?dz=mps1

Aldurazyme Information
http://www.aldurazyme.com/

National MPS Society
-www.mpssociety.org
If you have additional questions regarding MPS I or other lysosomal storage disorders, call the Emory Lysosomal Storage Disease Center at (404)778-8565 or 1-800-200-1524, or fill out the information below, and fax this page to: FAX (404) 778-8562. Thank you.

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