What is Your Diagnosis?

**CHIEF COMPLAINT**
A 35 y.o. Hispanic female presents with the following history:
- Severe fatigue
- Chronic depression
- Chronic diarrhea
- Abdominal pain
- Proteinuria

**PAST MEDICAL HISTORY**
Patient reports an unremarkable medical history. Of interest, she notes having a “nervous stomach” that was attributed to a low tolerance to stress and remarks that she has never enjoyed outdoor activities. She grew up in southwest Texas and the outside temperatures were always too hot for her. Currently, the patient works as a computer programmer.

**PHYSICAL EXAM** - Small "petechiae-like" lesions on lower abdomen.

**FAMILY HISTORY**
See pedigree. Significant family history includes an older brother with kidney problems, a mother who was diagnosed with an "enlarged heart" at 35, and two maternal aunts with strokes in their early 40’s.

1. Your diagnosis for the proband is:
   A) Fabry Disease
   B) Systemic Lupus Erythematosis (SLE)
   C) Irritable Bowel Syndrome
   D) Chronic Fatigue Syndrome
   E) Hypochondria

2. Which of the following tests would you order on the patient to clarify her diagnosis?
   A) Enzyme analysis
   B) Gene sequencing of a specific gene
   C) Antibody testing
   D) Melatonin levels

3. If you could obtain samples on only one other family member to further characterize the patient’s diagnosis, which relative would you choose and which tests would you order?
   A) Enzyme analysis on patient’s mother
   B) Sequence analysis on patient’s brother
   C) Antibody tests of one maternal aunt
   D) Enzyme analysis with reflex testing to gene sequencing on patient’s brother

4. What is the most likely inheritance pattern of the disorder in your patient’s family?
   A) Multifactorial
   B) Sporadic
   C) Autosomal Dominant
   D) X-linked

Take the Genetic Challenge!

Test your knowledge of clinical genetics. We hope you find these cases interesting and educational. Questions or comments, please call: 1-800-366-1502 or visit us on the web at: www.genetics.emory.edu.

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FINAL DIAGNOSIS
Since you found the patient’s report of heat intolerance intriguing, you asked the patient more about her problems in the heat. You learned that the patient really doesn’t sweat and that most of her mother’s side of the family also doesn’t sweat. Remembering an interesting tidbit about lack of sweating in Fabry you read somewhere before (perhaps in “Take the Genetic Challenge” in May 2003), you investigated what testing to order for Fabry disease. When you looked in your reference books, it at first appears that Fabry disease would be an unusual diagnosis for your patient because she is female and Fabry disease is X-linked (question 4). However, a quick call to your local geneticist informed you that recent studies of women who are “carriers” or heterozygotes for Fabry can be symptomatic, ranging from very mild to severe. You also learned that the enzyme analysis of alpha-galactosidase A that is diagnostic in men is not as accurate in women. Accordingly, you ordered enzyme analysis of alpha-galactosidase A and sequence analysis of the alpha-galactosidase A gene (question 2). You asked the patient if her brother would be able to provide a blood sample for enzyme analysis and possible sequencing. You tell her that the reason to test her brother is that the enzyme analysis is diagnostic in men. If her brother is affected by Fabry disease it establishes the presence of Fabry disease in the family (question 3).

The results of the enzyme analysis on the patient are low normal levels of alpha-galactosidase; however a mutation in the alpha-galactosidase A gene confirms a diagnosis of Fabry disease in your patient (question 1). You next obtained baseline labs (a urine chemistry total protein and creatinine, cholesterol tests, and a 24 hour urine with creatinine clearance), echocardiogram, EKG, and a brain MRI. You offered appropriate diagnostic testing to all of the patient’s at-risk family members, referred them to a geneticist, and discussed enzyme replacement therapy. You reminded your patient that enzyme replacement therapy is not a cure; it is a life-long treatment that must be done every two weeks.

ABOUT FABRY DISEASE
First described in 1898 by dermatologists Anderson and Fabry, Fabry disease should be considered in males and females with acroparesthesias, angokeratomas, hypohidrosis, characteristic corneal and lenticular opacities, stroke, left ventricular hypertrophy, or renal insufficiency of unknown etiology. Fabry disease is a lysosomal storage disorder caused by a deficiency of a specific enzyme, alpha galactosidase A (AGA) and characterized by the deposition of globotriaosylceramide (GL-3) in the vascular endothelium. Fabry disease is inherited as an X-linked condition, and therefore primarily affects males. However, studies have found that heterozygote females who were once considered only “carriers” also can develop symptoms of Fabry disease that range from very mild to very severe. An affected male will transmit the gene to all of his daughters. Heterozygote females will have a 50% chance to transmit the gene in any pregnancy. If transmitted, sons will be affected, and daughters will be heterozygotes, like the mother. In females, the severity of symptoms can vary widely due to different patterns of X-inactivation in each individual.

Some of the more common symptoms of Fabry disease include:
• Chronic Fatigue
• Acroparesthesia (episodic pain in the extremities often described as burning and/or sharp pain)
• Anhidrosis or Hypohidrosis (complete inability or decreased ability to sweat)
• Angiokeratomas (purple or dark pink vascular cutaneous lesions) of the skin and groin area
• Other symptoms related to progressive microangiopathic obstructive failure of vascular beds in critical organ systems

• Depression
• Intolerance to extreme heat or cold
• Corneal opacities
• Postprandial pain
• Alternating diarrhea and constipation
• Renal disease leading to renal failure
• Hearing Loss
• Myocardial ischemia or infarction
• Concentric myocardial hypertrophy
• Premature stroke

CLINICAL OVERVIEW
Although atypical variants with an intermediate presentation have been described, there are two major phenotypes found in Fabry disease:

Classic Form - usually found in males with <1% alpha-galactosidase A (AGA) activity who present in childhood (average age at onset 4-8 years) with acroparesthesia, appearance of angiokeratoma, hypohydrosis, characteristic corneal and lenticular opacities, and proteinuria. Deterioration of renal function to end-stage renal disease usually occurs in the third to fifth decade (average age of death 41 years). After renal transplant, most males then have progressive cardiovascular and/or cerebrovascular disease.

Cardiac Variant - males with 1-10% AGA activity, usually presents in the sixth to eighth decades with LVH, myocardial infarction, and/or cardiomyopathy. They usually do not develop end stage renal disease.

Heterozygous Carrier Females – females with low to normal AGA enzyme activity. Sometimes asymptomatic throughout a normal life-span, however, many manifest symptoms of the disease with increasing age. It is unknown what percentage of female carriers exhibit symptoms of Fabry, but some studies suggest it may be as high as 75%.

Because Fabry disease presents with such a wide and varied spectrum of symptoms, the disorder is often misdiagnosed or diagnosed late, after end-organ damage such as renal failure, myocardial infarction or premature stroke has already ensued. This disease is progressive with symptoms becoming more severe with increasing age in affected males and heterozygote females; therefore, early diagnosis with prompt and appropriate treatment with enzyme replacement therapy may prevent progression to irreversible damage of organs.

DIAGNOSIS
The least invasive and most cost-effective method of diagnosing Fabry disease in males is by AGA activity in plasma, leukocytes, and/or cultured cells. In females, this measurement is not reliable due to lyonization (the phenomenon by which one X-chromosome is randomly inactivated in early embryonic cells, with fixed inactivation in all descendent cells, first described by geneticist, Mary Lyons), as some carrier females have normal AGA activity. Clinical DNA testing (gene sequencing) for the alpha galactosidase A gene, called the GLA gene, located on Xq22, is available for females. Nearly all affected males and heterozygote females will have an identifiable mutation in the GLA gene. Over 300 mutations have been described in the GLA gene, with most mutations “private” (i.e. they have been found in only a single family).

PATHOPHYSIOLOGY
All Fabry patients have a deficiency of the enzyme alpha-galactosidase A. This enzyme functions in the lysosomes of cells to break down and remove glycolipids. Insufficient levels of AGA cause the glycolipid globotriaosylceramide (GL-3; also known as GB-3, ceramide trihexoside, or CTH), to accumulate in the lysosomes of virtually all body cells and tissues, particularly neurons, as well as renal, smooth muscle, cardiac, and vascular endothelial cells. Most of the GL-3 forms from cellular components of degrading erythrocyte membranes. As GL-3 accumulates, the vascular endothelium both narrows and dilates the blood vessels, causing ischemia and infarction that results in cell and organ damage.
FREQUENCY
The incidence of Fabry disease is estimated at 1 in 40,000 males and 1 in 20,000 females. The disease is present in all ethnic, racial, and demographic groups. This condition may be more common than originally estimated, as milder forms of Fabry disease involving the renal system, cardiovascular system, or neurological system alone may be mistaken for conditions other than Fabry.

TREATMENT
While there is no cure for Fabry disease at this time, enzyme replacement therapy is available. In the United States, Fabrazyme® enzyme replacement therapy (agalsidase beta) has been approved by the FDA. Fabrazyme® enzyme replacement therapy reduces globotriaosylceramide (GL-3) deposition in the capillary endothelium of the kidney, heart, and skin, and provides an exogenous source of AGA in Fabry disease patients. A Fabry Registry has been established for patients to better understand the variability and progression of Fabry disease and to monitor the long-term treatment effects of Fabrazyme® (www.fabryregistry.com).

If you have additional questions regarding Fabry disease, please call Emory Genetics 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. Additional information at: www.genetics.emory.edu/genservices/lsdc

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