EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of Human Genetics
Division of Medical Genetics
Lysosomal Storage Disease Center
www.genetics.emory.edu

Fabry Disease and the Kidneys©2005

What is Fabry Disease?

Fabry disease (FD) is an X-linked genetic disease caused by a deficiency of the enzyme α-galactosidase A (α-Gal A) in the body. The enzyme α-Gal A's function is to break down a fatty substance called globotriaosylceramide (or GL3). When α-Gal A is absent, GL3 builds up in the blood vessel walls throughout the body. As the abnormal storage of GL3 increases with time, the body's blood vessels become narrowed, leading to decreased blood flow and undernourishment of the tissues. This abnormal process occurs in various cell types and in blood vessels throughout the body, particularly those blood vessels in the skin, kidneys, heart, brain and nervous system. The early symptoms of Fabry disease, which usually begin in childhood, include decreased sweating, heat intolerance, proteinuria, a reddish-purple skin rash (angiokeratoma), severe pains in the hands and feet, hearing loss, chronic fatigue, depression, anxiety, and gastrointestinal issues such as chronic diarrhea. Fabry disease symptoms affect both women and men. Since the disease is progressive, untreated Fabry disease results in many severe health problems such as kidney failure, heart problems including enlargement of the left side of the heart (left ventricular hypertrophy) and valve disease, and cerebrovascular problems such as stroke and vertigo. Not every person with Fabry disease will have all the same symptoms of disease progression; however, without treatment the disease always gets worse over time. (2)

Where are the kidneys and what do they do?

The kidneys are bean-shaped organs located near the middle of your back. The kidneys are sophisticated reprocessing machines. Every day, a complicated chemical exchange takes place in your kidneys, as waste materials and water leave your blood and enter your urinary system. Your health care team may talk about the work your kidneys do which is called renal function. If you have two healthy kidneys, you have 100 percent of your renal function. You will have serious health problems if you have less than 25 percent of your renal function. If your renal function drops below 10 to 15 percent, you cannot live long without some form of renal replacement therapy—either dialysis or transplantation.(6)

What effect does Fabry disease have on my kidneys and their function?

The kidney problems in Fabry disease occur from the progressive accumulation of globotriaosylceramide (GL3) in the cells of the kidney. The accumulation of GL3 causes the kidneys to lose their ability to filter waste and chemicals in your body. The accumulation of GL3 gradually leads to total or nearly total and permanent kidney failure called end-stage renal disease (ESRD). People with ESRD must undergo dialysis or transplantation to stay alive.

How is kidney function measured?

In order to monitor and evaluate kidney function in Fabry disease, a series of kidney function tests including urinary protein, urinary creatinine, serum creatinine, glomerular

filtration rate (GFR), and 24 hour urine are needed at least every year. The test for urinary protein tells us whether or not the kidneys are damaged and allowing big proteins to pass through the kidneys' filters into the urine. As kidney function worsens, the amount of proteins in the urine increases. This condition is called proteinuria. Creatinine is a waste product in the blood created by the normal breakdown of muscle cells during activity. Healthy kidneys take creatinine out of the blood and put it into the urine to leave the body. When kidneys are not working well, creatinine builds up in the blood. If your creatinine level is only slightly above the normal range, you probably will not feel sick; however, the elevation is a sign that your kidneys are not working at full strength. GFR is a calculation of how efficiently the kidneys are filtering wastes from the blood. A twenty-four hour urine sample gives the protein excretion rate, the creatinine excretion rate, and GFR over 24 hours. [6] In some instances, a physician may choose to do a renal biopsy to examine the amount of GL3 built up in the kidney cells.

What symptoms might indicate my kidney function is worsening?

People in the early stages of kidney disease usually do not feel sick at all. The first sign of a kidney problem may be high blood pressure, a low number of red blood cells (anemia), or blood or protein in the urine. If your kidney disease gets worse, you may need to urinate more or less often. You may feel tired or itchy. You may lose your appetite or experience nausea and vomiting. Your hands or feet may swell or feel numb. You may get drowsy or have trouble concentrating. Your skin may darken. You may have muscle cramps. [6]

What can be done to help prevent Fabry disease from damaging my kidneys?

Begin enzyme replacement therapy (ERT) early - ERT is therapy designed to replace the missing α-galactosidase A in individuals affected by Fabry disease. ERT involves an intravenous (IV) infusion every other week with enzyme made of purified alpha-galactosidase A enzyme. Research studies found that over time a dose of 1 mg/kg every other week clears GL3 out of the kidney to normal or near-normal levels in 98% of subjects affected by Fabry disease.[3] When GL3 is removed from the kidneys, they should work more effectively. ERT is the only therapy for Fabry disease that addresses the underlying problem of GL3 accumulation in the kidney.

Work with a nephrologist - A nephrologist is a doctor who specializes in the kidneys and their function. They are the experts most qualified to discuss medications, kidney function, and treatment options with you.

Consider other medications - In addition to ERT, individuals with proteinuria and/or high blood pressure may be prescribed blood pressure lowering medicines called angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).[8] These medications have been found to protect the kidneys and decrease the amount of protein in the urine. The National Heart, Lung, and Blood Institute recommends that people with diabetes or reduced kidney function should keep their blood pressure below 130/80 mm Hg. [1]

Stop Smoking - Smoking increases the risk for kidney failure, strokes, heart attacks, lung cancer, and respiratory illness. Since individuals with Fabry disease are already

at increased risk for stroke, heart attack, kidney failure, and lung problems, they should stop smoking.

Change Your Diet - People with reduced kidney function need to be aware that some parts of a normal diet may speed their kidney failure. Some doctors tell their kidney patients to limit the amount of protein, cholesterol, potassium, and/or sodium they eat so that the kidneys have less work to do. You may need to work with a dietitian to find the right food plan. [5]

I'm on dialysis now, how does this affect my treatment plan? AND
Why didn't ERT stop my kidney function from worsening?

If an individual is affected by Fabry disease and begins ERT with elevated creatinine levels or in end stage renal disease, permanent damage to kidney cells has already occurred. In these cases, the ERT cannot stop kidney failure, but can hopefully prolong kidney function and reduce the chance for complications related to cardiac problems and strokes. Just as in individuals without Fabry disease, if your kidneys stop working correctly, you will need to undergo dialysis or kidney transplantation. If you choose to pursue dialysis, in order to remove the wastes from your body, dialysis must be attended exactly as recommended by your nephrologist.

In the past, when an individual with Fabry Disease reached the point of needing dialysis, they did very poorly. In one study, three year after dialysis began in Fabry patients, only 60-63% of patient were still living.[7] Combining dialysis with continued ERT does improve the survival rate by helping the heart, preventing strokes, and continuing to remove GL3 from the body. Depending on the dialysis center, some individuals will be able to receive ERT and dialysis at the same time. Having said this, kidney transplant combined with ERT is often the best therapy for Fabry patients with end stage renal disease. [7] Please remember, individuals affected by Fabry disease who are being given a kidney from a relative, must make sure that the kidney donor is not affected by Fabry disease.

Is ERT beneficial in individuals after a kidney transplant?

Yes. The residual enzyme in a donor kidney will prevent GL3 from building up in the transplanted kidney. The enzyme present in a transplanted kidney can protect itself, but cannot prevent GL3 from building up in the other cells of the body. Accordingly, individuals affected by Fabry disease still need ERT to prevent accumulation of GL3 in their the heart, blood vessels, and other cells in your body. Studies of ERT in individuals after transplant indicate that ERT is safe and effective against non-kidney related complications of Fabry disease.[4]

Where can I learn more about kidney function, kidney disease, and kidney function in Fabry disease?

National Kidney Foundation
30 East 33rd Street, New York, NY 10016
Phone: 1–800–622–9010 or 212–889–2210
Internet: http://www.kidney.org
NKF Fabry fact sheet: http://www.kidney.org/atoz/atozItem.cfm?id=61

National Kidney and Urologic Diseases Information Clearinghouse 3
Information Way, Bethesda, MD 20892–3580
Email: nkudic@info.niddk.nih.gov
http://kidney.niddk.nih.gov/kudiseases/a-z.asp

Where can I learn more about Fabry disease and enzyme replacement therapy?
Fabry Support & Information Group (FSIG)
108 NE 2nd Street, Suite C, P.O. Box 510
Concordia, MO 64020
Phone: (660) 463-1355
Internet: http://www.fabry.org/

The Fabry Community
An informational website about Fabry disease and ERT produced by Genzyme
Internet: http://www.fabrycommunity.com/

The Emory Lysosomal Storage Disease Center
2165 North Decatur Road
Decatur, GA 30033
Phone: 404-778-8565 or 800-200-1524
Internet: http://www.genetics.emory.edu/genservices/lsdc.php

References:

1. Bakris GL, Williams M, Dworkin L, National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: A consensus approach. Am J Kidney Dis. (2000) 36:646-661.

2. Desnick RJ, R Brady, J Barranger, AJ Collins, DP Germain, M Goldman, G Grabowski, S Packman, and WR Wilcox. Fabry Disease, an Under-Recognized Multisystemic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy. Ann Intern Med. (2003) 138:338-346.

3. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S., et al. Safety and efficacy of recombinant human α-galactosidase A- replacement therapy in Fabry's disease. N Engl J Med. (2001) 345; 9-16.

4. Mignani, R., V. Panichi, A. Giudicissi, D. Taccola, F. Boscaro, C. Feletti, G. Moneti, and L. Cagnoli. Enzyme Replacement with agalsidase beta in kidney transplant patients with Fabry disease: A pilot study. *Kidney International*, (2004) 65:1381-1385.

5. National Kidney Foundation. About Chronic Kidney Disease: A Guide for Patients and their Families. Updated 6/9/2005. http://www.kidney.org/atoz/atozItem.cfm?id=145.

6. National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK is part of the National Institutes of Health NIH Publication No. 03–4241. updated July 2003.
http://kidney.niddk.nih.gov/kudiseases/pubs/yourkidneys/

7. Sessa, A, M Meroni, G. Battini, M. Righetti, and R. Mignani. Chronic Renal Failure Dialysis, and Renal Transplantation in Anderson-Fabry Disease. Seminars in Nephrology (2004) 24:532-536.

8. Warnock, David. Fabry disease: diagnosis and management, with emphasis on the renal manifestations. Curr Opin Nephrol Hypertens. (2005) 14:87-95.