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CASE REPORT

Female with Fabry Disease Unknowingly Donates Affected Kidney to Sister: A Call for Pre-transplant Genetic Testing

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Abstract Fabry disease, an X-linked lysosomal storage disorder, is caused by the deficiency of the alpha-galactosidase A enzyme and the progressive accumulation of globotriaosylceramide in vascular endothelial cells. The multi-systemic manifestations of Fabry disease include cardiac, gastrointestinal, renal, and neuropathic complications. Renal dysfunction and ultimately end-stage renal disease occurs in classically affected males and in about 10–15% of female heterozygotes from classically affected families as a result of progressive glycosphingolipid accumulation. We report a case in which a female with a de novo *GLA* mutation donated a kidney to her sister prior to the diagnosis of symptomatic Fabry disease. The transplant recipient has progressed to graft failure and has been relisted for transplant. This case report demonstrates the need to screen potential kidney transplant donors and recipients for Fabry disease.

Abbreviations
ESRD End-stage renal disease

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Introduction

Fabry disease is an X-linked genetic disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A. The *GLA* gene is the only known gene to be associated with Fabry disease. Deficiency of alpha-galactosidase A leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide, in vascular beds throughout the body. Progressive lysosomal deposition of globotriaosylceramide in the vascular endothelium ultimately leads to clinically significant disease, affecting the cardiovascular system, kidneys, skin, gastrointestinal system, and neurological system (Zarate and Hopkin 2008). The most severe clinical manifestations of Fabry disease include cardiomyopathy, stroke, and progressive renal insufficiency leading to end-stage renal disease (ESRD). Patients with Fabry disease may present with gastrointestinal symptoms, such as diarrhea, abdominal pain, and bloating, as well as neurological symptoms such as acroparathesias, heat or cold intolerance, tinnitus, hearing loss, and hypohidrosis. Cardiovascular evaluation may reveal electrocardiographic abnormalities, valvular disease, and left ventricular hypertrophy. Angiokeratomas, especially around the umbilicus and inguinal area, may also be present.

Manifestation of Fabry disease is often more severe in men due to the very low residual function of alpha-galactosidase A. Affected women may have later onset of disease due to random X-inactivation or Lyonization causing variable expression of alpha-galactosidase A. Interestingly, Fabry disease in women has been recognized to cause frequent major organ involvement (Ojo et al. 2000; Thadhani et al. 2002; Wilcox et al. 2008) and to benefit from enzyme replacement therapy (Whybra et al. 2009). Activity levels of alpha-galactosidase A can be diagnostic for males but mutation testing should be performed in

females to confirm heterozygous status, since enzyme activity measurements may vary (Linthorst et al. 2005). While Fabry disease was initially thought to be rare (~1:40,000), recent studies suggest that milder forms of the disease that present later in life and primarily affect the cardiovascular, cerebrovascular, or renal system may be more common and may be underdiagnosed. This is highlighted by a recent newborn screening study in Italy that demonstrated an incidence of Fabry disease as high as 1:3,100 (Spada et al. 2006).

ESRD remains a major cause of morbidity and mortality in this population and management of patients with Fabry disease prior to and following transplantation can be challenging. Enzyme replacement therapy has been shown to provide both renal and cardiovascular benefit in patients with Fabry disease (Banikazemi et al. 2007; Eng et al. 2001) and potentially provides a means to halt the progressive kidney disease in this population. Although Fabry disease and other hereditary nephropathies should be considered prior to kidney transplantation (Niaudet 2010), there is only a formal protocol to screen for autosomal dominant polycystic kidney disease and Alport's syndrome in living donors (Kasiske et al. 1996). Deceased donor screening for Fabry disease mainly relies on medical history and assessment of laboratory measures of kidney function. While patients have previously received transplantation of a kidney from patients with Fabry disease (Kochar et al. 2011; Popli et al. 1987; Puliyanda et al. 2003; Schweitzer et al. 1992), we describe the case of a female with symptomatic de novo Fabry disease that was identified years after donation of a kidney to her sister.

Patient History

We present the case of a 44-year-old Caucasian female referred to our Genetics Clinic for evaluation of Fabry disease after the discovery of bilateral corneal whorling during routine ophthalmologic examination. Exposure to medications that can induce corneal opacities such as amiodarone, chloroquine, indomethacin, or phenothiazine was ruled out. At 34 years of age, she donated a kidney to her younger sister who had developed ESRD secondary to Type 1 diabetes mellitus. The patient's workup prior to the kidney donation demonstrated a normal electrocardiogram, normal pulmonary function tests, a normal computed tomography angiogram with normal renal vasculature, and normal laboratory values at the time of kidney donation, with no proteinuria. Her past medical history was significant for mild intermittent asthma treated with a bronchodilator as needed, allergic rhinosinusitis treated with daily loratadine and pseudoephedrine, and three prior episodes of uncomplicated cystitis. Her history was negative for any prior cardiovascular or cerebrovascular events. Aside from kidney donation, her surgical history is only significant for tonsillectomy at the age of 7 and right ovarian cystectomy at the age of 22. The patient has no known allergies and was not on any other medications. She is married and has no children. Her review of systems was positive for occasional pain in her fingers and toes that she described as a "pricking" feeling. She reported normal sweating and denied heat or cold intolerance. She admits to fatigue but attributed this to her occupation. She admits to night sweats that she believes are related to the onset of menopause. She has tinnitus in her right ear but denies hearing loss. She denied any gastrointestinal symptoms. Physical examination was unremarkable and negative for angiokeratomas. Enzyme and molecular testing confirmed the diagnosis of Fabry disease and revealed that the patient carries a c.952delG mutation in the *GLA* gene (Mount Sinai Genetic Testing Laboratory). Her alpha-galactosidase A activity level was decreased at 8.04 nmol/h/mg (normal range 12.8–74.1) in leukocytes and 2.00 nmol/h/ml (normal range 6.2–18.6) in plasma (Mount Sinai Genetic Testing Laboratory).

Two months following our evaluation, the patient was hospitalized for left-sided facial weakness and upper extremity tingling. An MRI of the brain demonstrated no evidence of acute cerebral infarct, but there were chronic ischemic changes within the deep white matter and periventricular region, particularly more prominent in the bilateral temporal and occipital region. A transthoracic echocardiogram demonstrated moderate left ventricular hypertrophy, along with papillary muscle hypertrophy, a left ventricular ejection fraction of 70% without wall motion abnormalities, and mild mitral regurgitation. Cardiac MRI demonstrated moderate left ventricular hypertrophy with an anterior wall thickness of 1.3 cm, a posterior wall thickness of 1.2 cm, a septal wall thickness of 1.3 cm, and a lateral wall thickness of 1.2 cm. There was no evidence of delayed contrast enhancement on T1 weighted imaging, suggesting the absence of myocardial fibrosis or deposition. Serum creatinine and 24-h urine creatinine were within normal limits but LDL cholesterol was elevated at 141 mg/dl. She was treated with aspirin, an angiotensin-converting enzyme inhibitor, a beta-blocker, and a statin.

The patient's younger sister is a 39-year-old female with a history of Type I diabetes mellitus diagnosed at the age of 5. By 29 years of age, this sister had progressed to ESRD. She initiated hemodialysis and later underwent a living-donor kidney transplant, receiving her older sister's kidney. She underwent pancreatic transplant a year later. Since that time, her kidney transplant has failed and she is currently relisted for renal transplant. She has a surgical history also significant

for surgery for diabetic retinopathy, cataract surgery, appendectomy, and bilateral oophorectomy secondary to ovarian cysts. She denied cardiovascular or cerebrovascular events including stroke or myocardial infarction. She is followed by a cardiologist and has mild left ventricular hypertrophy. She has had prior syncopal episodes, lightheadedness, and occasional heart palpitations. She complains of neuropathy of the hands and feet, hypohidrosis, and is easily overheated. She denied hearing loss or tinnitus. She has gastroparesis, chronic diarrhea, and abdominal pain and bloating. She does not have any angiokeratomas. She is single and has no children. We obtained blood for enzyme and molecular testing for Fabry disease of both which were normal (Mount Sinai Genetic Testing Laboratory). She does not have the deletion found in her sister. Her alpha-galactosidase A activity level was 29.91 nmol/h/mg (normal range 12.8–74.1) in leukocytes and 9.40 nmol/h/ml (normal range 6.2–18.6) in plasma (Mount Sinai Genetic Testing Laboratory).

The parents of the Proband are divorced and little is known about her father's family. The father was not available for molecular and enzymatic analysis. He has Type 2 diabetes mellitus and he has two sisters who are alive and well. Paternity to both sisters was confirmed by the mother. The sisters' mother has a history of cataracts and wears glasses. She has no known corneal whorling. She has an occasional "pricking" feeling around her ribs and along her arms when she is hot. She has mild hearing loss in the left ear, tinnitus, and high blood pressure. The sisters had a maternal uncle who died at 21 years from nephritis. Their maternal grandmother died at 82 years from stomach cancer. She had a history of "silent strokes." Their maternal grandfather died of a heart attack and had a history of emphysema. There is no reported history of mental retardation, birth defects, multiple miscarriages, or other genetic disorders in the family. There is no known consanguinity. Subsequent enzyme and molecular testing for Fabry disease were performed in the mother of these sisters and were both normal (Mount Sinai Genetic Testing Laboratory). The alpha-galactosidase A activity level was 29.45 nmol/h/mg (normal range 12.8–74.1) in leukocytes and 10.20 nmol/h/ml (normal range 6.2–18.6) in plasma and no mutation was found (Mount Sinai Genetic Testing Laboratory). Thus, both the mother and sister of the Proband lack the disease-causing mutation and do not have Fabry disease.

Discussion

Despite an extensive evaluation at the time of transplant, patients with undiagnosed Fabry disease may lack specific laboratory findings or symptoms that would raise the concern for this diagnosis. Given the preference for living-donor transplants due to HLA compatibility, patients with ESRD and known Fabry disease should have extensive screening of family members with enzyme testing of males and enzyme and molecular testing for females to avoid transplantation of an affected kidney (Niaudet 2010; Popli et al. 1987; Puliyanda et al. 2003; Schweitzer et al. 1992) into patients with Fabry disease. It is important to further highlight this as kidney transplantation from affected sisters into males with Fabry disease was reported long ago (Groth and Ringden 1984; Popli et al. 1987; Schweitzer et al. 1992). While a combination of ophthalmologic screening and enzyme testing has been utilized in the past (Bloomfield et al. 1978; Schweitzer et al. 1992), molecular screening provides the greatest level of sensitivity to diagnose heterozygote females (Linthorst et al. 2005). The transplantation of an affected kidney into patients with Fabry disease not only leads to premature graft failure (Popli et al. 1987; Puliyanda et al. 2003) but may also adversely impact renal function of the affected donor. Additionally, patients with ESRD have been shown to have an increased prevalence of Fabry disease (Nakao et al. 2003) and the clinical diagnosis of Fabry disease can be missed in patients undergoing kidney transplantation (Kleinert et al. 2009). Thus, given the increased risk of adverse cardiovascular and cerebrovascular events in patients with Fabry disease and the availability for treatment with enzyme replacement therapy, patients with ESRD should be screened for Fabry disease prior to transplantation, especially since patients with undiagnosed Fabry disease may then receive living-donor transplantation from an affected relative.

Our case highlights the importance of screening donors for Fabry disease prior to living-donor kidney transplantation. While a case of a deceased-donor kidney transplantation demonstrated Fabry disease of the renal allograft (Kochar et al. 2011), screening for Fabry disease in the case of deceased-donor kidney transplantation with enzyme and molecular analysis is not practical, given time constraints. Therefore screening would in large part depend on histopathological analysis of the renal allograft. As the mother did not have the mutation and the Proband's sister was spared, her father most likely did not harbor the mutation since Fabry disease is X-linked. Therefore, the deletion in our patient likely represents a de novo event. However, it is still possible that either the mother or the father could be a germ line mosaic for the mutation. Although our patient with Fabry disease currently has normal renal function, the possible long-term risk of renal dysfunction associated with kidney donation in heterozygous females is significant (Niaudet 2010). Popli and colleagues

reported a case of a heterozygous Fabry female who donated a kidney to a male relative and had a significant decline in renal function within 5 years after donation (Popli et al. 1987). Additionally, the donation of a kidney from a heterozygous Fabry female raises the question of whether receiving a kidney from an individual who harbors a Fabry mutation with decreased enzyme activity and prior globotriaosylceramide accumulation could contribute to premature graft failure in a sibling whose renal disease is unrelated to Fabry disease. Thus, donation of a kidney would not be recommended in patients known to carry a *GLA* mutation.

The incidence of Fabry disease in not only patients with ESRD, but also the general population, is likely to be much higher than previously estimated. This is supported by newborn screening which demonstrated Fabry disease in 1 in 3,100 live births (Spada et al. 2006). As this is not the first case of Fabry disease in a renal allograft (Kochar et al. 2011; Popli et al. 1987; Puliyanda et al. 2003), there is clearly a need to evaluate whether all kidney transplant recipients and living donors should undergo enzymatic and molecular testing for Fabry disease prior to transplantation. A potential protocol for screening of Fabry disease might include detailed family and medical history, in conjunction with alpha-galactosidase enzyme testing in males and molecular genetic testing for females. Although demonstration of decreased alpha-galactosidase A activity is diagnostic of the heterozygote state in a female, between 33 and 40% of females with Fabry disease diagnosed by molecular analysis have normal alpha-galactosidase A activity (Linthorst et al. 2008; Linthorst et al. 2005) and thus alpha-galactosidase A activity is unreliable for the diagnosis of Fabry disease in females. If cost were prohibitive, an alternative approach for females might be enzyme testing in conjunction with a slit-lamp ophthalmological exam looking for corneal findings. However, molecular genetic testing of *GLA* is the most reliable method for the diagnosis of affected females.

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Disclosure

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