Natural History and Treatment of Renal Involvement in Fabry Disease

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Renal involvement has been recognized as a complication of Fabry disease since the original reports by Anderson and Fabry in the late nineteenth century. Clinical involvement of the kidney typically begins before age 30 in male patients, although exceptions occur. In female carriers, the variability in renal involvement in considerable, with many women lacking clinically apparent renal disease and others with severe kidney disease (1). We have recently reviewed the natural history of renal involvement in 105 male Fabry patients who have been seen at the National Institutes of Health (NIH) over a 30-yr period (2). The development of recombinant α-galactosidase A (α-Gal A) as a therapeutic agent offers the exciting possibility of slowing the progression of this devastating renal disease. In this review, we will provide an overview of the manifestations and natural history of renal disease and review the evidence from recently published clinical trials that α-Gal A enzyme replacement therapy has a favorable effect on the kidney.

Diagnosis

The diagnosis of Fabry renal disease is often made by recognition of extrarenal manifestations. In the NIH series, a known family history of Fabry disease contributed to the diagnosis in 46% of patients. In patients lacking a family history, the diagnosis of Fabry disease was made by dermatologists (28%), neurologists (23%), rheumatologists (2%), and cardiologists (2%). In 19% of cases, the diagnosis was made by nephrologists, most often by renal biopsy.

The diagnosis of Fabry renal disease should be suspected in a young male patient (as well in women of any age, although female carriers [heterozygotes] are less commonly affected than men) who presents with impaired urinary concentrating ability and proteinuria or chronic renal insufficiency. This is particularly true if the patient gives a history of neuropathic pain, decreased sweating, or abdominal pain or diarrhea or has typical angiokeratomas on the skin (see article in this issue by Pastores and Lien). A family history suggesting similar symptoms in male family members is helpful but may not be present in every case.

The nephrologist can perform careful examination of the urine sediment, looking for oval fat bodies and lipid droplets with a lamellar pattern and Maltese cross pattern under polarized microscopy. Urinary excretion of globotriaosylceramide (Gb3), also known as ceramide trihexoside (CTH), is another useful approach to diagnosing Fabry disease in a patient with unexplained kidney disease in whom other symptoms and signs suggest the disorder. Close examination of the skin may demonstrate angiokeratomas, most prominent in a bathing suit distribution; these are nonblanching, reddish papules that are a few millimeters in diameter. In some patients, the angiokeratomas may be restricted to the scrotum and are easily missed if not carefully sought. A slit lamp exam may show corneal opacities that are virtually diagnostic of Fabry disease (especially in female heterozygotes), and tortuous blood vessels may be present in the sclera and retina, which is not a specific finding. Biopsy of either involved or uninvolved skin is a relatively noninvasive way to make the diagnosis; specific identification of glycolipid deposits using lectin histochemistry may be helpful (see article in this issue by Alroy et al.). A readily available test is the measurement of residual α-gal A activity in leukocytes, plasma, or cultured skin fibroblast; the value is typically <12% of normal in a male hemizygote and more variable in female heterozygotes (see article in this issue by Pastores and Lien). Several academic laboratories offer mutation analysis of the α-Gal A gene, although this is not commercially available at present. A renal biopsy may not be necessary to confirm Fabry renal disease if the presentation and family history are typical and the diagnosis of Fabry has been clearly established in a family member.

Functional Renal Defects

Urinary concentration defects may be the earliest functional manifestation of Fabry renal disease, leading to polyuria and nocturia. Nephrology referral is more typically initiated by the development of proteinuria. Proteinuria may begin in the teenage years and becomes more frequent when patients reach their 20s and 30s. In the NIH series, 33 of 34 patients who had urine protein electrophoresis were found to have glomerular proteinuria, although the proteinuria did not usually reach nephrotic levels. Indeed, 23% of patients progressed to chronic renal insufficiency (CRI) without ever having nephrotic proteinuria. The full presentation of nephrotic syndrome was not frequent even in those patients who developed nephrotic-range proteinuria. Only 26% of

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patients with nephrotic-range proteinuria developed hypoalbuminemia, and 21% developed hyperlipidemia.

The onset of CRI may begin as early as the second decade of life (Figure 1). The mean age of onset of clinical nephropathy (CRI or proteinuria) has been reported as 27 yr (3). In the NIH series, we found from survival analysis that 50% of patients developed CRI by 43 yr of age.

End-stage renal disease (ESRD) was the most common cause of death in Fabry patients before the development of dialysis and renal transplantation, when uremic death occurred at a mean age of 41 yr (4). ESRD may rarely occur during the teenage years (5). In the NIH series, we found from survival analysis that 50% of patients developed ESRD by 53 yr, with a range of 21 to 56 yr (Figure 1). Overall, 24 (23%) of 105 of patients developed ESRD; this represents a minimum estimate, as some patients in the study will likely develop ESRD in the future (see article in this issue by Obrador et al.). Importantly, all NIH patients who have lived into their 50s have developed ESRD, although the number of patients is relatively small and exceptions may still occur.

It is worth considering the relationship between the prevalence of Fabry disease and the number of patients who enter the United States Renal Data System (USRDS) database with a diagnosis of Fabry disease. The frequency of Fabry disease is estimated to range between 1:40,000 and 1:117,000 male births (6) (also see the article in this issue by Grünfeld et al.), suggesting that 1000 to 3500 men in the United States have this disease. Extrapolating from the 23% minimum prevalence of ESRD in the NIH study would suggest that at least 250 to 800 men in the United States who are alive today will eventually develop ESRD due to Fabry disease. Assuming a 50-yr average lifespan and population equilibrium, one would predict that approximately 5 to 15 Fabry patients would reach ESRD each year. This agrees fairly well with the observed rate in the USRDS database of approximately 14 patients per year (7).

Progression from onset of CRI to ESRD occurred in NIH patients over a mean of 4 ± 3 yr (range, 1 to 13 yr) and was not affected by patient age at onset of CRI or magnitude of proteinuria. Relatively few patients had received angiotensin-converting enzyme (ACE) inhibitors or angiotensin II antagonists, so we could not evaluate the efficacy of these agents in slowing disease progression; there are no published reports that address this issue. The mean rate of decline in GFR was 12.2 ml/min per yr in nine patients (Figure 2). This rate of renal functional decline is comparable to that seen in diabetic nephropathy in patients not receiving angiotensin antagonist therapy (8) and faster than a number of other renal diseases, including many forms of glomerulonephritis.

Interestingly, hypertension does not appear to be a major contributing factor in this rapid progression, as only 30% of the 105 NIH patients developed hypertension at any time in their lives. The 35% of those patients who developed hypertension did so before the onset of CRI; 12% developed hypertension simultaneously with CRI, and 53% developed hypertension a mean of 5 ± 5 yr after the onset of CRI. Angiotensin antagonist medications (ACE inhibitors and angiotensin receptor blockers) were used by only 19% of NIH patients, as many of these patients were seen before the availability of these medications. In the NIH series, 18 patients have died. No patient in this series has survived past 60 yr of age.

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**Figure 1.** Kaplan-Meier analysis of probability of developing renal syndromes, hypertension, and death. The proportion of patients surviving without chronic renal insufficiency (CRI, \( n = 82 \)) and hypertension (\( n = 105 \)), end-stage renal disease (ESRD, \( n = 82 \)) are shown, as well as the proportion that remains alive (\( n = 105 \)). (Replotted from the data presented in Figure 2 of Branton et al. (2), used with permission).
Patients with undetectable residual α-Gal A activity had higher scores for glomerular pathology ($P = 0.027$) and tubulointerstitial pathology ($P = 0.007$), and they also had higher concentrations of Gb3 in kidney tissue ($P = 0.039$).

The type and possibly the location of mutation may also influence the age of onset of CRI in Fabry patients. Residual α-Gal A activity and clinical course of renal disease were evaluated in 47 patients from the NIH series for whom genetic sequencing had been performed. Patients were divided into (1) those with conservative missense mutations in which one amino acid residue is substituted by another amino acid of the same structural class (acid, basic, polar, hydrophobic straight chain, hydrophobic ring form, or special), (2) those with nonconservative substitution mutations, and (3) those with nonconservative mutations that involved deletion, insertion, or a premature stop codon. Patients who had conservative substitution mutations ($n = 6$) had higher residual α-Gal A activity (6.8 ± 4.8% of normal) and maintained normal renal function during the period of follow-up. By contrast, patients with nonconservative substitution mutations ($n = 16$) had lower mean residual α-Gal A activity (1.0 ± 2.1%), and CRI had developed in 5 patients beginning at age 22. Similarly, patients with other nonconservative mutations had still lower mean residual α-Gal A activity (0.8 ± 1.4%) and earlier onset of CRI. Figure 3 presents survival analysis for the onset of CRI, comparing patients with conservative mutations and all nonconservative mutations. Intriguingly, earlier CRI was seen in patients with mutations in exons 3, 6, and 7 compared with patients with mutations in exons 1, 2, and 5 (there were no patients with mutations in exon 4), although the numbers were too small for statistical analysis.

### Treatment

Fabry patients with proteinuria or CRI should have aggressive treatment of hypertension if it is present and should probably be treated with angiotensin antagonist therapy; the latter recommendation is based on theoretical considerations, as proof of efficacy has not been attempted.

Schiffmann and colleagues carried out a double-blind, randomized, placebo-controlled study of recombinant a-Gal A produced in a human cell line (Replagal; Transkaryotic Therapies, Cambridge, MA) and administered by biweekly infusion to 26 male Fabry patients for 6 mo (9). The primary endpoint of this study was a reduction in neuropathic pain. Significant reductions in the severity of “pain at its worst” and in the use of chronic pain medications were demonstrated. Enzyme replacement therapy was associated with relatively few side effects, chiefly mild transient infusion reactions, which became uncommon when the infusion duration was increased (from 20 to 40 min).

Histologic assessment of renal biopsy samples, read in a masked fashion and then assessed as paired samples, showed that enzyme therapy was associated with more normal glomerular and tubulointerstitial pathology.
uli (*P* < 0.01) and fewer glomeruli exhibiting mesangial matrix widening (*P* < 0.01), as well a slight increase in segmentally sclerotic glomeruli (*P* < 0.05) and no change in the number of globally sclerotic glomeruli. There were relatively few globally sclerotic glomeruli; therefore, the overall effect was an improvement in glomerular architecture. There was no change in the composite scores for tubulointerstitial damage or glycolipid deposits (the latter was assessed on toluidine blue-stained sections as the sum of scores in podocytes, glomerular endothelial/mesangial cells, proximal tubular epithelial cells, distal tubular epithelial cells, extraglomerular vascular endothelial cells, and vascular medial cells). Interestingly, there was however a significant decrease in glycolipid deposits in vascular endothelial cells (*P* < 0.002). Enzyme replacement therapy was associated with a significant fall in Gb3 concentrations in plasma and urine sediment, but the findings in kidney tissue biopsies were NS (although a trend was present).

With respect to the effect of enzyme replacement therapy on renal function, there was a trend toward a greater fall in GFR measured by inulin clearance with placebo compared with enzyme therapy (*P* = 0.27). There was a 16 ml/min fall in creatinine clearance observed in the placebo group versus a 2 ml/min rise in creatinine clearance in the enzyme group, a difference that was statistically significant (*P* = 0.005). When urinary under-collections and over-collections were accounted for, some of this statistical significance was attenuated (*P* = 0.05). Furthermore, the mean drop in GFR in the patients receiving placebo (20 ml/min over 6 mo by inulin clearance, 16 ml/min over 6 mo by creatinine clearance) was larger than expected from our previous natural history experience (although the number of patients is greater than that in the natural history study) and included some patients with initially normal or elevated GFR. Six months of enzyme therapy had no consistent effect on proteinuria. Preliminary data from open-label extension of enzyme replacement in patients enrolled in the original trial showed that patients in the original treatment group continued to have stable or improved inulin and creatinine clearance after 18 mo of enzyme therapy. In contrast, patients originally in the placebo group who had shown a decline in renal function demonstrated significantly improved inulin clearance and creatinine clearance after 12 mo of enzyme replacement therapy (10). Improved intracardiac conduction as evidenced by significant reduction of QRS complex duration after 6 mo of enzyme treatment was also noted (see article in this issue by Kampmann et al.). These early results with enzyme replacement are encouraging, and results of continued therapy will be interesting to follow.

Eng et al. (11) evaluated the efficacy of recombinant human α-Gal A produced in Chinese hamster ovary cell line (Fabrazyme; Genzyme, Boston, MA) in Fabry patients. In an open-label, dose-ranging study involving 15 patients, these authors found that biweekly infusions given for 10 wk was associated with reduced kidney Gb3 content (5 of the 15 patients underwent paired renal biopsies; no statistics given). On glutaraldehyde-fixed, methylene blue-stained kidney biopsy tissue, there was reduced storage material in interstitial capillary endothelial cells and mesangial cells. There was a lesser degree of improvement or no improvement in tubular epithelial cells and glomerular podocytes. These results were used to design a double blind, randomized placebo-controlled trial involving 58 male Fabry patients treated with biweekly intravenous infusions for 20 wk, with the primary endpoint being clearance of interstitial capillary endothelial cell deposits (12). Complete clearance of interstitial capillary endothelial cell deposits occurred in 20 of 29 of α-Gal A–treated patients and 0 of 29 placebo-treated patients (*P* < 0.001). Similar changes in endothelial cell deposits were seen in skin and heart capillaries. There was no beneficial effect on GFR assessed by inulin clearance. There was a transient improvement in pain scores that did not persist to week 20, but pain results were no different than with placebo.

In summary, two placebo-controlled clinical trials have shown that 6 mo of enzyme replacement therapy with α-Gal A is associated with improved glomerular architecture and/or reduced glycolipid deposits in the kidney, and one study (NIH) also suggested improvement in renal function. The two trials have recently been reviewed (13). It makes sense that vascular endothelial cells are especially responsive to intravenously administered enzyme, in that these cells have direct access to the α-Gal present in the circulation. The majority of Gb3 deposition in the kidney, however, does not appear to be within these cells. Indeed, Schiffmann et al. also demonstrated improved glomerular architecture, and results of follow-up studies of renal function are forthcoming. Additional studies as to whether α-Gal A therapy can prevent, slow, halt, or reverse declining renal function in patients with Fabry disease will likely be of 1 yr or longer duration, possibly selecting only patients with renal insufficiency for inclusion to maximize the chance of showing a benefit in renal function. Nevertheless, at the present time enzyme replacement therapy holds considerable promise for patients with Fabry disease with and without kidney involvement.

**References**


