March 2002 - Volume 81 - Issue 2

- Previous Article
- Next Article

Article

Natural History of Fabry Renal Disease

Influence of α-Galactosidase A Activity and Genetic Mutations on Clinical Course

BRANTON, MARY H. M.D.; SCHIFFMANN, RAPHAEL M.D.; SABNIS, SHARDA G. M.D.; MURRAY, GARY J. PH.D.; QUIRK, JANE M. M.S.; ALTARESCU, GHEONA M.D.; GOLDFARB, LEV PH.D.; BRADY, ROSCOE O. M.D.; BALOW, JAMES E. M.D.; AUSTIN, HOWARD A. III M.D.; KOPP, JEFFREY B. M.D.

Author Information

From the Metabolic Diseases Branch (MHB, JEB, HAA, JBK), National Institute of Diabetes and Digestive and Kidney Disease, Developmental and Metabolic Neurology Branch (RS, GJM, JMQ, GA, ROB), and Clinical Neurogenetics Unit (LG), National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, and the Armed Forces Institute of Pathology (SGS), Washington, DC.

Address reprint requests to: Jeffrey B. Kopp, MD, 10/3N116, NIH, Bethesda, MD 20892-1268. Fax: 301-402-0014; e-mail: jbkopp@nih.gov.

Medicine 81(2):p 122-138, March 2002.

- Free

Introduction

Fabry disease is an X-linked sphingolipidosis caused by complete or partial deficiency of the glycohydrolase α-galactosidase A (α-gal A) ([4]). The enzyme deficiency results in accumulation of globotriaosylceramide (Gb3, also known as ceramide trihexoside), as well as digalactosyl ceramide and blood group B, B1, and P1 glycolipids in the lysosomes of vascular endothelial, smooth muscle, epithelial, and ganglion cells. The metabolic defect causes a painful neuropathy, angiokeratomas, cardiac and cerebrovascular injury, and renal failure. Hemizygous males usually experience multisystem involvement with symptoms beginning in childhood or infancy, although oligosymptomatic (usually cardiac) variants are reported ([25,37,40,60]). Heterozygous females have more variable expression due to random X chromosome inactivation, with some patients experiencing few

or mild symptoms, and others developing skin, ocular, and renal manifestations, premature strokes, and myocardial infarctions, although usually later in life than affected males.

Renal involvement has been recognized as a cardinal feature of Fabry disease since patients with characteristic skin lesions and albuminuria were first described in 1898 ([2,17]). The kidney pathology of renal involvement has been described as vacuolated epithelial cells and podocytes in the glomerulus and distal tubules ([6,10]). Lipid inclusions appear as clusters of intracellular vacuoles by conventional light microscopy, but exhibit dense osmiophilic staining in epon-embedded material stained with toluidine blue in epithelial cells. Electron microscopy shows intracytoplasmic irregular lamellar bodies that are lysosomes containing Gb3. With time, the glomeruli develop mesangial widening and progressive sclerosis, tubular atrophy, and interstitial fibrosis. Decreased urinary concentrating ability may be the earliest apparent renal abnormality, with onset of proteinuria in early adulthood and onset of renal failure in the fourth to fifth decades of life. Before the advent of dialysis and renal transplant, the most common cause of death was uremia, at a mean age of 41 years ([11]).

Although there are accounts of individual patient presentations and follow-up of small kindreds, the rarity of Fabry disease has made evaluation of large groups of patients difficult to achieve. We reviewed the medical records of 105 male patients with Fabry disease. We describe the clinical course and histology of their renal disease and correlate them with residual α-gal A activity and with mutations in the α-gal A gene. Diagnosis of Fabry disease occurred later in patients without a known family history. Fifty percent of patients developed proteinuria by age 35 years and chronic renal insufficiency (CRI) by age 42 years. We found that detectable residual α-gal A activity was associated with a slower progression of Fabry renal disease, and with lower scores for renal histologic damage and renal Gb3 content. Conservative mutations in the α-gal A gene were also associated with slower progression of Fabry renal disease.

Patients and Methods

Definitions (

Table 1)

TABLE 1:
Definitions

Conditions are defined in Table 1. Hypertension was classified according to the sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure ([53]). For patients on antihypertensive therapy, control was considered to be a systolic blood pressure ≤130 mmHg and diastolic blood pressure ≤90 mmHg.

Data collection

We reviewed the clinical records of 105 male Fabry patients who were evaluated at the Warren Grant Magnuson Clinical Center of the National Institutes of Health, Bethesda, Maryland, (NIH) from 1970 to 2000. All patients were enrolled in clinical protocols approved by the appropriate Institutional Review Board. The diagnosis of Fabry disease was made by the presence of the typical symptoms and signs of neuropathic pain, angiokeratoma, diarrhea and abdominal pain, proteinuria and renal failure, ocular abnormalities, or early stroke. In all patients, the clinical diagnosis was confirmed by demonstration of leukocyte α-gal A activity <15% of the value in healthy volunteers. In 49 patients, determination of leukocyte α-gal A activity was performed at the NIH, and in the remainder of the patients it was performed at another institution.

Clinical data collected included the onset of clinical manifestations of Fabry disease, interval between earliest recalled symptoms and diagnosis of Fabry disease, blood pressure, age and cause of death, and serum creatinine, serum albumin, and cholesterol. At the NIH, monitoring of serum creatinine and urinary protein excretion in a semiquantitative or quantitative fashion was carried out during routine follow-up, which was usually at least annually. Data on renal function, clinical, and urinary findings from other institutions were usually forwarded to the NIH at the time of referral. In some cases, we contacted local physicians to obtain additional history of Fabry-related symptoms, physical examination, and laboratory data (serum creatinine, urine protein) that were collected both before and following the diagnosis of Fabry disease. Data concerning renal tubular function, such as urinary concentrating ability and the presence of urinary cells containing Fabry inclusion bodies, were not consistently available and were therefore not included in the present study. Death certificates were obtained for 12 of the 18 patients who died. A cohort of 25 patients participated in a randomized controlled trial of recombinant α-gal A that began in 1999. Patients were censored after the last date for which data were available, or the date on which they began to receive infusions of enzyme in the case of patients who participated in the α-gal A replacement trial.

From these data, we determined the age of onset of proteinuria, hypertension, and CRI, and rates of progression to nephrotic proteinuria and to end-stage renal disease (ESRD). We determined the cumulative percentage of patients attaining a given age who had reached an endpoint. This was determined using as the numerator the number of patients who had reached the endpoint by a particular age (patients either still alive or having died) and as the denominator the number of patients who had reached the indicated endpoint (patients either still alive or having died) or who were alive without having reached the indicated endpoint. No Fabry patient survived past age 60 years in our study.

We analyzed only patients for whom adequate data existed to diagnose a syndrome and to assign an age of onset for the syndrome. We had these data for 80 patients for proteinuria, 105 patients for hypertension, 82 patients for CRI, 82 patients for ESRD, and death for 105 patients. We included in the CRI and ESRD groups only those patients for whom the age of onset of both CRI and ESRD could be determined. Thus, while 24 of 105 patients developed ESRD in the entire study group, only 18 patients were included in the cumulative percentage analysis as developing ESRD. This was done because the 2 syndromes, CRI and ESRD, occur sequentially and we wished to show the timing of progression in the same patients. Thus, considering patients for whom adequate data were available, by 60 years of age, 66 patients had developed proteinuria, 34 patients had developed hypertension, 34 patients had developed CRI, 18 patients had developed ESRD, and 18 patients had died.

Rate of progression from CRI to ESRD

The mean time from onset of CRI to ESRD was determined for 15 patients for whom both the date of onset of CRI and the date of onset of ESRD were known. Glomerular filtration rate (GFR) was estimated by the 4-variable equation developed from data obtained as part of the Modification of Diet in Renal Disease study as validated by Levey et al (28a) (see Table 1). The correction factors for race or gender were not applicable to these 15 patients. GFR data at time of initiation of renal replacement therapy were defined as 12 mL/min if laboratory data were not available. Mean time from onset of CRI and mean rate of loss of GFR were determined from the data.

Renal pathology

Renal biopsies were performed in 25 of 26 male patients with Fabry disease who were enrolled in a trial of α-gal A replacement therapy ([51]). One patient did not have a biopsy due to the presence of extensive renal cysts. All biopsies were performed before the initiation of therapy. Patients were selected for the trial based on the presence of neuropathic pain, because this was the primary endpoint. Patients with ESRD were excluded from participation, but there was otherwise no selection for renal function. Baseline inulin clearance was 87 ± 29 mL/min/1.73 m^2, with a range of 20–160 mL/min/1.73 m^2. Five patients had normal protein excretion; 17 patients had subnephrotic proteinuria, and 3 patients had nephrotic proteinuria. Renal biopsy specimens were read in a blinded fashion by 2 renal pathologists, who determined a consensus histology score for each biopsy.

Glomerular numbers were counted in paraffin and plastic sections. The number of glomeruli per biopsy was 26 ± 15 (range, 2–57; only 1 biopsy had <8 glomeruli). The mesangial architecture of each glomerulus was classified as follows: a) normal (score = 0), b) diffuse mesangial widening throughout the capillary tuft (score = 1), c) segmental sclerosis or solidification (score = 2), d) global sclerosis or glomerular obsolescence (score = 4). Glomeruli classified as normal showed no evidence of mesangial widening or sclerosis, but could contain lipid inclusions. The numerical fraction of glomeruli in these 4 categories was determined. The glomerular pathology score was determined by summing the individual scores and dividing by the glomerular number; a score of 0 would denote all glomeruli normal and a score of 4 would denote all glomeruli obsolescent.

The raw tubulointerstitial pathology score was determined as a sum of the following 5 parameter scores, each rated on a scale of 0–3: tubular atrophy, interstitial inflammation, interstitial fibrosis, vascular medial thickening and vascular hyalinosis. The tubulointerstitial pathology score was determined by dividing the sum of the raw tubulointerstitial pathology scores by 5. One biopsy had insufficient tissue for analysis.

Glycolipid inclusions were assessed by examination of toluidine blue stained semi-thin plastic sections. The raw glycolipid inclusion score was calculated as a sum of scores for the following 6 cellular compartments, each rated on a scale of 0–3: glomerular epithelial cells, glomerular endothelial/mesangial cells, proximal tubular epithelial cells, distal tubular epithelial cells, vascular endothelial cells, and vascular medial cells. The raw glycolipid score was divided by 6 to generate the glycolipid score. One patient had insufficient tissue for analysis.

Gb3 analysis

Gb3 was determined in plasma, urine, and renal biopsy tissue by high-performance liquid chromatography in the 26 patients enrolled in the α-gal A therapy trial as described previously ([52]). Plasma Gb3 was expressed as nmol/mL of plasma, urine Gb3 was expressed as nmol/g of urine creatinine, and renal tissue Gb3 was expressed as nmol/mg of wet weight kidney tissue.

α-gal A assay

Fluorometric assay of residual α-gal A activity was performed as previously described ([27]). Briefly, peripheral blood leukocytes were sonicated in an aqueous buffer (28 mM citric acid, 44 mM disodium phosphate, 5 mg/mL sodium taurocholate, pH 4.4) and then centrifuged at 20,000 g for 30 min. Total α-gal A activity was determined by incubating aliquots of the supernatant solution at 37 °C with 10 mM 4-methylumbelliferyl-α-D-galactopyranoside (Research Products International, Mount Prospect, IL) in the same buffer without taurocholate and with added bovine serum albumin (5 mg/mL). 4-methylumbelliferyl-α-D-galactopyranoside is a substrate for both α-gal A and α-gal B. α-gal B activity is blocked in the presence of the competitive inhibitor N-acetylgalactosamine, and this confers specificity in the determination of residual α-gal A activity. α-gal A activity was expressed as a percentage ratio between patient α-gal A and healthy volunteer α-gal A assayed on the same day. Each result was the mean of 3 determinations. Residual α-gal A activity values <1% were considered undetectable.

Genetic mutation analysis

DNA was obtained from fibroblasts or whole blood. All 7 exons of the α-gal A gene were amplified by PCR using primers derived from flanking intron sequences, and the DNA sequence was determined in 47 patients ([1]). Residual α-gal A activity and onset of renal insufficiency were compared in patients with conservative and nonconservative mutations.

Statistics

Data are presented as mean ± standard deviation. Data that were normally distributed were analyzed using the Student t test, or the Welch t test when standard deviations were different among groups. Data that were not normally distributed were analyzed using Wilcoxon rank sum test. Differences in frequencies were subjected to the Fisher exact test. For t test analyses in which groups had differing α-gal A activity or different classes of α-gal A mutations, a 1-tailed t test was employed. Kaplan-Meier plots showing differences in the age of onset of renal syndromes were evaluated by the 1-tailed Mantel-Cox test. A p value of <0.05 was accepted as significant. Statistical software included Instat (Graphpad, San Diego, CA), and BMDP Statistical Software (Berkeley, CA).

Results

Population and demographics

Of 105 hemizygous male patients, 94 patients were Caucasian, 8 patients were Hispanic, 1 patient was African-American, 1 patient was Native American, and 1 patient was Asian. Blood group data were available for 63 patients, of whom 27 (43%) were blood group A, 3 (5%) were blood group B, and 33 (52%) were blood group O. This was not different from the distribution of blood groups in the Caucasian population of North America ([28]).

Eighteen patients have died; the mean age at death was 50 ± 8 years. Death certificates were available for 12 patients and showed the following causes of death: pulmonary embolism, 2; sepsis, 2; cerebrovascular accident, 1; cardiac failure, 1; myocardial infarction, 1; respiratory failure, 1; lung carcinoma, 1; acute ethanol poisoning, 1; suicide, 1; and unknown, 1.

Diagnosis of Fabry disease (

Figure 1)

F1-3
Fig. 1:
Age at onset of clinical manifestations and diagnosis of Fabry disease. The number of patients in each decade of life is shown for earliest recalled onset of Fabry symptoms (black bars), and for age at Fabry diagnosis (white bars).

We investigated the clinical findings that led to the diagnosis of Fabry disease in all 105 patients. Forty-four patients were diagnosed with Fabry disease because of known family history, either through prenatal or early childhood screening, or because another family member undergoing evaluation at the same time as the patient was diagnosed. In these patients, the age of diagnosis was 16 ± 13 years (range, prenatal to 40 yr). Fifty patients lacked a family history of Fabry disease. For these patients the age of diagnosis was 28 ± 12 years (range, 18 mo–55 yr, $p < 0.0001$), which was significantly higher than that observed among patients with a family history of Fabry disease. These patients recalled experiencing clinical symptoms for 15 ± 13 years before diagnosis (range, 0–40 yr) (Figure 1). For 11 patients, it was not clear whether family history contributed to diagnosis. In patients without a family history of Fabry disease, the diagnosis was first made by dermatologists (28%), ophthalmologists (26%), neurologists (23%), nephrologists (19%), rheumatologists (2%), and cardiologists (2%). Medical diagnoses considered before recognition of Fabry disease included fever of unknown origin, malabsorption syndromes, inflammatory bowel disease, inflammatory arthropathies. The presence of unexplained chronic pain resulted in some patients being considered malingerers or narcotic-seekers.

Proteinuria (

Figures 2, 7F, 7G)

F2-3
Fig. 2:

Cumulative percentage of patients developing renal syndromes, hypertension, and death with increasing age. The cumulative percentage of patients by age who developed the indicated syndrome is shown. The total number of patients included in the analysis differed among the syndromes (as described in Methods): 80 for proteinuria, 105 for hypertension (HTN), 82 for chronic renal insufficiency (CRI), 82 for end-stage renal disease (ESRD), and 105 for death. Twenty-five patients survived to age 50 years, 12 patients survived to age 55, and no patients survived past age 60 years.


Fig. 7:

Renal pathology in fabry disease **A.** Glomerulus showing extensive inclusion bodies of glycolipid in podocytes (arrowhead), and mild mesangial widening (PAS stain, original magnification × 80). **B.** Plastic embedded tissue showing in site deposition of glycolipid in glomerular podocytes (arrowhead, toluidine blue stain, original magnification × 80). **C.** Plastic embedded renal tissue demonstrating glycolipid inclusion bodies in distal tubules (arrowhead), with relative sparing of proximal tubules, and interstitial fibrosis (toluidine blue stain, original magnification × 80). **D.** Deposition of glycolipid in endothelial cells of peritubular capillaries (arrowhead; asterisk is in lumen of proximal tubule, toluidine blue stain, original magnification × 200). **E.** Artery showing glycolipid inclusions in endothelial cells (arrowhead) and smooth muscle cells (arrow, toluidine blue, original magnification × 80). **F.** Urine showing vacuolated urinary epithelial cells (oval fat bodies) in a Fabry patient (Papanicolaou stain, original magnification × 160). **G.** Urinary glycolipid from a Fabry patient viewed through crossed polarizing filters; 1 lipid droplet shows both the Maltese cross conformation typical of lipid and the lamellar appearance of Fabry glycolipid (arrowhead).

Seventy-eight of 105 patients had proteinuria and/ or CRI, which constituted clinical evidence of renal disease. Proteinuria was present at some time in the clinical course of 66 of 78 patients with renal disease. The age of onset of non-nephrotic proteinuria was 34 ± 10 years (range, 14–55 yr). Fifty percent of all Fabry patients developed proteinuria by age 35 years, and 100% of surviving patients developed proteinuria by age 52 (Figure 2).

Nephrotic proteinuria was found in 19 of 78 (18%) patients with renal disease. Daily protein excretion was 5.6 ± 3.6 g/day (range, 3–8 g/day) in these 19 patients. The age at onset of nephrotic proteinuria was 40 ± 7 years (range, 26–55 yr). In those patients who developed CRI, nephrotic proteinuria appeared before the onset of CRI in 18%, after the onset of CRI in 18%, and was never present in 23%; adequate data for magnitude of proteinuria in later stages of disease were lacking in 40%. Only 5 of 19 patients (26%) with nephrotic proteinuria had serum albumin <3.5 g/dL at peak proteinuria, and only 4 of 19 (21%) had serum cholesterol >200 mg/dL. Thus, the full presentation of nephrotic syndrome was uncommon even in patients who had heavy proteinuria. In some patients, the presence of oval fat bodies in urine with both a Maltese cross and lamellar pattern may suggest the diagnosis of Fabry disease (see Figures 7F, 7G). Regardless of the magnitude of proteinuria, in 33 of 34 patients for whom urine protein electrophoresis was performed the proteinuria was of glomerular origin (≥50% albumin). One patient had tubular proteinuria (<30% albumin).

Chronic renal insufficiency and end-stage renal disease (

Figures 2, 3)


Fig. 3:

Distribution of rates of decline in glomerular filtration rate (GFR). The rate of loss of GFR in - mL/min/yr is shown for 14 patients for whom the times of onset of both chronic renal insufficiency and end-stage renal disease are known. The mean rate of loss was −12.2 ± 8.1 mL/min/yr (range, −3.3 to −33.7 mL/min/yr), indicated by the bar.

Thirty-nine of 105 patients developed CRI. The median age of CRI onset was 42 years (range, 19–54 yr) among the 33 patients for whom data for age of onset were available. Twenty-four patients developed ESRD at a median age of 47 years (range, 21–56 yr). Time of progression from onset of CRI to ESRD was 4 ± 3 years (range, 1–13 yr) in 14 patients for whom ages of onset of both CRI and ESRD were available (Figure 3). Linear regression analysis indicated no effect of patient age at onset of CRI or maximal magnitude of proteinuria upon the rate of progression. There were insufficient data on residual enzyme activity and too few serial measurements of blood pressure to perform regression analysis for these variables.

In Figure 4, plots of 1/serum creatinine versus time are presented for 9 patients with Fabry disease who had progressive renal failure and for whom at least 4 determinations of serum creatinine were available. All of these patients have generally similar rates of progression. One patient who progressed to ESRD after approximately 1 year of follow-up had a rate similar to other patients, when the 1/creatinine value at entry is considered. Three patients, including the patient who progressed to ESRD within a year, had mild or easily controlled hypertension.


Fig. 4:
Progression of renal insufficiency. Renal function, expressed as the reciprocal of serum creatinine, is plotted against time, expressed as years from onset of chronic renal insufficiency, defined as a sustained serum creatinine ≥1.5 mg/dL. Data represent 9 patients for whom at least 4 serial serum creatinine values were available over a period extending from the onset of chronic renal insufficiency to the onset of end-stage renal disease.

Twenty-four of 105 (23%) patients developed ESRD. All patients in our study who survived to the age of 55 years developed ESRD (see Figure 2).

Fourteen patients began hemodialysis at the onset of ESRD, and 6 patients began peritoneal dialysis. For 4 patients the mode of dialysis could not be determined from available records. Of the 10 ESRD patients who did not receive renal transplants, 6 were treated with hemodialysis only and 3 received peritoneal dialysis; the mode of dialysis was unknown for 1 patient. Six patients have been treated with hemodialysis for 5.8 ± 6.4 years (range, <1–17 yr). One of these patients died after 17 years on hemodialysis, and another was lost to follow-up after 10 years on hemodialysis, demonstrating that prolonged survival on dialysis is possible in Fabry disease. Two patients received peritoneal dialysis for 2 and 3 years before death, respectively, and 1 patient has been treated with peritoneal dialysis for 4 years until the present.

Hypertension

Of 105 Fabry patients, hypertension was present in 31 (30%), with onset at age 38 ± 11 years (range, 14–54 yr). At onset of hypertension, 14 of 31 hypertensive patients (45%) had stage I hypertension, and 6 of 31 hypertensive patients (19%) had stage II hypertension. Eleven patients (36%) had medically controlled hypertension for which the original stage could not be determined.

We examined the relationship between the onset of hypertension and the onset of CRI, since CRI due to any cause is commonly associated with hypertension. Seventeen of 105 patients (16%) developed both hypertension and CRI. Six of 17 (35%) patients developed hypertension before the onset of CRI, 2 of 17 (12%) patients had a simultaneous diagnosis of hypertension and CRI, and 9 of 17 (53%) patients developed hypertension 5 ± 5 years after the onset of CRI.

We examined the role of angiotensin antagonist medications, either angiotensin converting enzyme inhibitors or angiotensin receptor blockers, as a possible factor in modifying the course of renal disease. Use of these medications was not frequent. Eighteen of 105 patients (19%) received an angiotensin antagonist at any time. Indications for angiotensin antagonist therapy included hypertension without renal abnormalities (6 patients), hypertension with proteinuria (1 patient), hypertension with established CRI (5 patients). Angiotensin antagonist therapy was started for proteinuria without hypertension in 3 patients, and for congestive heart failure in 1 patient. For 2 patients, the indication for angiotensin antagonist therapy could not be determined.

Renal transplant

Fourteen patients underwent 15 kidney transplants. One patient received a renal transplant from a living related donor, and the remainder received cadaveric renal transplants. The age at first renal transplant was 38 ± 9 years. Seven patients received renal transplants after 14 ± 5 months (range, 12–24 mo) on hemodialysis, and 3 patients received renal transplants after 22 ± 12 months (range, 12–36 mo) on peritoneal dialysis. One patient was treated with both hemodialysis and peritoneal dialysis for 1 year before renal transplantation. Three patients received renal transplants preemptively or after an unknown method of dialysis.

Ten patients had stable allograft function for 10 ± 9 years (range, 1–28 yr) following transplant. Of these, 2 patients died with well-functioning allografts at 12 and 28 years after kidney transplant, respectively; the causes of death were metastatic lung cancer and cardiac failure. One of these patients had a first renal transplant at age 23 years with rapid allograft rejection and at age 24 received a second renal transplant, which functioned well for 28 years. One patient developed chronic allograft nephropathy and returned to dialysis after 8 years. One patient died with chronic renal allograft failure at 11 years posttransplant and another died of pulmonary embolism 6 years posttransplant. The remaining kidney transplant recipient was lost to follow-up.

Two patients had renal transplant biopsies. One biopsy, performed 13 years after renal transplant, showed acute cellular and vascular rejection that responded to adjusted immunosuppressive therapy; no evidence of Fabry inclusions was found by light microscopy, and electron microscopy was not performed on this tissue. The other biopsy, performed 7 years posttransplant, showed chronic allograft nephropathy and no evidence of Fabry inclusions by either light or electron microscopy.

Three patients reported an increase in sweating after renal transplantation. One patient reported an increase and 1 reported a decrease in neuropathic pain after renal transplant, but there was otherwise little effect of renal transplantation on extrarenal symptoms of Fabry disease.

Renal syndromes correlated with residual α-gal A activity (

Figures 5 and 6)

F5-3
Fig. 5:
Distribution of residual α-galactosidase A (α-gal A) activity. α-gal A activity was measured in leukocytes obtained from 49 male Fabry patients, and is expressed as percentage of α-gal A activity measured in healthy volunteers. α-gal A activity was undetectable in 31 patients and was 1%–12% of normal control activity in the other 18 patients.

F6-3
Fig. 6:
Onset of chronic renal insufficiency: effect of level of α-galactosidase A (α-gal A) activity. The probability of normal creatinine (<1.5 mg/dL) is expressed as a function of age in Fabry patients with undetectable levels of α-gal A activity (open square) and in Fabry patients with ≥1% α-gal A activity (closed square). The number of patients with follow-up data at each age is shown. Age of onset of chronic renal insufficiency was significantly later in patients with detectable α-gal A activity ($p = 0.005$).

Residual α-gal A activity was determined at the NIH in 49 patients; assays performed at other institutions were not included in this analysis. Thirty-one patients had undetectable α-gal A activity and 18 patients had residual α-gal A activity between 1% and 12% of normal control activity. We compared the age of onset of CRI in patients with undetectable α-gal A activity and the age of onset of CRI in those with residual α-gal A activity ≥1% and found them to be different (Figure 6, $p = 0.005$). In the former group, the earliest CRI onset was 22 years; in the latter group, the earliest CRI onset was 47 years. By the age of 55 years, all surviving patients with undetectable residual α-gal A activity had developed CRI, whereas 2 patients with residual α-gal A activity ≥1% retained

normal renal function. The age of onset of proteinuria was not different between the 2 groups (data not shown). Only 3 of the 49 patients who had determinations of residual α-gal A activity reached ESRD, all of whom had undetectable α-gal A activity; this difference between the groups did not reach significance (data not shown).

Renal pathology: Correlation with residual α-gal A activity (

Figures 7, 8, Table 2)

T2-3
TABLE 2:
Renal function, renal pathology, and glycolipid determination

F8-3
Fig. 8:
Electron micrograph showing lamellar osmiophilic inclusions in glomerular visceral epithelial cell (arrowheads). The asterisk is in the lumen of a glomerular capillary. Arrow indicates intact foot process (original magnification × 20,000).

Quantitative analysis was performed on renal biopsy tissue from 25 patients. By light microscopy, the mildest changes consisted of vacuolization of the visceral glomerular epithelial cells and distal tubular epithelial cells consistent with Fabry inclusion changes. Later changes included expansion of the mesangium. In some patients segmental glomerulosclerosis and global glomerulosclerosis (progressing to an obsolescent glomerulus) were seen. With more advanced disease, distal and occasional proximal tubules manifested inclusions and the interstitium showed fibrosis. Arteries and arterioles were characterized by inclusions in endothelial and vascular smooth muscle cells, more so in arteries than in arterioles; glomerular and peritubular capillaries had inclusions in endothelial cells.

Linear regression analysis of pathology scores with patient age showed no significant influence of age upon pathology scores in the tubulointerstitial compartment ($r = 0.22$, $p = 0.3$) or upon glycolipid inclusions ($r = 0.28$, $p = 0.21$), but age did correlate modestly with glomerular pathology scores ($r = 0.42$, $p = 0.036$).

Measurement of α-gal A activity was available for 21 of 25 patients who had quantitative analysis of renal biopsies (Table 2). Renal pathology scores were compared between 14 patients who had undetectable α-gal A activity and 7 patients who had residual α-gal A activity ≥1%. Age was not different between the 2 groups (37.4 ± 7.6 yr versus 35.1 ± 7.2 yr, $p = 0.6$). Glomerular pathology scores were higher (1.11 ± 0.79) in patients with undetectable α-gal A activity compared to patients with α-gal A activity ≥1% (0.61 ± 0.32, $p = 0.027$). Tubulointerstitial pathology scores were also higher (0.24 ± 0.20) in patients with undetectable α-gal A activity compared to patients with residual α-gal A activity ≥1% (0.07 ± 0.10, $p = 0.007$). Glycolipid inclusion scores were similar in patients with undetectable α-gal A (0.53 ± 0.10) and in patients with α-gal A activity ≥1% (0.48 ± 0.21, $p = 0.62$).

Ultrastructural evaluation of renal biopsy tissue demonstrated typical osmiophilic lamellar inclusions in glomerular epithelial cells and vascular endothelium. These were not subjected to quantitative analysis.

Quantitative analysis of Gb3 in plasma, urine, and tissue (

Table 2)

Plasma and urinary Gb3 levels were similar in patients with detectable residual α-gal A activity and patients with undetectable α-gal A activity (see Table 2). Kidney Gb3 tissue levels were 14.4 ± 7.5 nmol/mg in patients with detectable α-gal A activity compared with 21.6 ± 8.4 nmol/mg in patients with undetectable α-gal A activity; this difference was statistically significant ($p = 0.039$).

α-gal A mutations: Correlation with enzyme activity and onset of CRI (

Tables 3, 4;Figures 9, 10)

T3-3
TABLE 3:
Missense mutations

T4-3
TABLE 4:
Mutations: Premature stop codons, deletions, and insertions

F9-3
Fig. 9:
Onset of chronic renal insufficiency: effect of α-galactosidase A (α-gal A) gene mutation subtype. The proportion of patients with normal serum creatinine (<1.5 mg/dL) is expressed as a function of age in 6 Fabry patients with conservative mutations in the α-gal A gene (closed triangle) and in 15 patients with nonconservative mutations in the α-gal A gene (open triangle). Patients with conservative mutations had a later onset of chronic renal insufficiency (p = 0.045).

F10-3
Fig. 10:
Onset of chronic renal insufficiency by exon location of mutation. Kaplan-Meier plot showing survival with normal renal function plotted by the exon location of mutation. Patients with >1 mutation are excluded.

Genetic sequencing of the coding region of the α-gal A gene was performed in 47 patients. At least 1 mutation was identified in every patient; there were 36 different mutations, and 3 patients had 2 mutations. Of these mutations, 21 have been previously reported and 15 were novel ([1]). The clinical course of renal disease was defined for all 47 patients, and measurements of residual α-gal A activity were available for 31 patients.

Most of the patients who shared mutations were closely related as indicated in Tables 3 and 4. An exception is 4 patients from Nova Scotia who have no known common ancestor, but share a substitution mutation.

α-gal A activity was 6.78% ± 4.75% of normal in patients with conservative substitution mutations and was 0.99% ± 2.09% in patients with nonconservative substitution mutations (see Table 2, p = 0.03). All 6 patients with a conservative amino acid substitution mutation have so far maintained a normal serum creatinine during follow-up, although some have developed proteinuria. By contrast, CRI has developed in 5 of 16 patients with a nonconservative amino acid substitution mutation, first appearing at age 22 years (p = 0.05).

We also compared residual α-gal A activity and clinical course in patients with conservative substitution mutations and patients with all other mutations (nonconservative substitution mutations, premature stop codons, insertions, and deletions). Residual α-gal A activity was higher in patients with conservative amino acid substitutions (6.78% ± 4.75%) compared to those with all nonconservative mutations (0.81% ± 1.45%, p = 0.029). Patients with conservative substitution mutations had delayed onset of CRI compared to patients with all nonconservative mutations (Figure 9, p = 0.045).

We analyzed the effect of the exon location of mutations on residual α-gal A activity and age of CRI onset. Conservative mutations were confined to exon 1 (1 patient), exon 2 (2 patients), and exon 5 (3 patients). Since we observed that the conservative mutations were associated with higher α-gal A activity and later CRI onset, we excluded these patients from further analysis. Nonconservative mutations were found in 38 patients, distributed as follows: exon 1 (5 patients), exon 2 (1 patient), exon 3 (11 patients), exon 5 (6 patients), exon 6 (4 patients), and exon 7 (11 patients). No patient had a mutation in exon 4. Three patients who had more than 1 coding region mutation were not included in this analysis. As shown in Figure 10, mutations in exons 3, 6, and 7 were associated with progression to CRI during the time of study, whereas no patient with mutations in exons 1, 2, or 5 had yet developed CRI. While the number of patients is too small to analyze, these data suggest that mutations in exons 3, 6, and 7 may particularly affect progression of renal disease. Residual α-gal A activity was higher in

patients with mutations in exons 1, 2, or 5 compared with patients who had mutations in exons 3, 6, or 7 (3.3 ± 4.1 versus 0.64 ± 1.4, p = 0.013).

Discussion

In this study we describe the clinical spectrum of renal involvement in 105 patients with Fabry disease evaluated at the NIH over the past 25 years. We have analyzed the impact of residual α-gal A activity and α-gal A mutations on the course of renal disease. α-gal A replacement therapy may soon be available for Fabry patients and may have a favorable impact on the course of renal disease ([51]). Therefore, a review of the natural history of renal involvement in Fabry disease would be useful to define the typical course and predictive factors of Fabry renal disease.

Proteinuria and renal failure have been considered cardinal manifestations of Fabry disease for over 100 years. There have been many case reports ([6,32,41]), series comprising 3–12 patients ([10,22]), and reviews ([34]) describing Fabry renal disease. Male hemizygotes are almost invariably affected. Female heterozygotes are less commonly affected, but due to random inactivation of the X chromosome, they may in some cases manifest severe renal disease.

The urine sediment in Fabry disease may contain oval fat bodies, which are renal tubular epithelial cells or cell fragments with lipid inclusions. Under microscopy using crossed polarization filters, these oval fat bodies demonstrate a typical Maltese cross configuration, but unlike the oval fat bodies in nephrotic syndrome of other etiologies, these have a lamellar appearance. In addition, electron microscopic examination of the urine from Fabry patients with renal involvement demonstrates characteristic lamellar osmiophilic inclusions in urinary cells. This has been proposed as a diagnostic aid, particularly in the evaluation of family members ([56]).

Renal tubular function is frequently compromised in Fabry patients. Distal tubular function is particularly susceptible, resulting in impaired urinary concentration ([6]). Proximal tubule dysfunction has been reported more rarely, with reduced tubular threshold for the reabsorption of glucose and amino acids and an incomplete renal tubular acidosis ([41]).

Proteinuria typically provides the first evidence of renal functional impairment in Fabry disease, appearing in our patients at a mean age of 34 years. Proteinuria tends to become progressively heavier with time, and reaches nephrotic levels in 18% of patients with evidence of renal disease. In 40% of nephrotic Fabry patients, nephrotic proteinuria appears only after the onset of CRI or may be entirely absent during the course of renal disease. In nearly all cases of proteinuria, the urine contained abundant albumin and was therefore of glomerular origin. Hypoalbuminemia and hypercholesterolemia were generally absent despite nephrotic-range proteinuria. It can be hypothesized that in the absence of hypoalbuminemia, there is no stimulus for accelerated cholesterol synthesis, but the relative infrequency of hypoalbuminemia in these patients is not fully explained. Normal levels of serum albumin have been reported in nephrotic proteinuria associated with glomerular hyperfiltration, whereas hypoalbuminemia is typical of nephrotic lesions due to primary glomerulopathies ([46]).

Hypertension in Fabry patients might have at least 3 possible etiologies: it may be a consequence of renal insufficiency, a consequence of Fabry-associated vascular disease, or it may be a process unrelated to the Fabry disease, such as the coincident presence of essential hypertension in a patient with Fabry disease. We found that hypertension was not a prominent finding in this population and frequently did not appear until patients had declining renal function. Hypertension was found in only one-third of patients, half of whom also developed CRI. In 65% of hypertensive Fabry patients, the hypertension did not appear until the onset or well after the onset of CRI or ESRD. This, together with the mean overall age of onset late in the fourth decade, suggests that the hypertension is more likely essential, or secondary to established renal disease. In some Fabry patients, renovascular disease can cause hyperreninemic hypertension ([49]).

The average age of the onset of clinical nephropathy in male Fabry patients has been reported to be 27 years ([14]). While the definition of clinical nephropathy was not provided, this likely represents the appearance of either proteinuria or renal insufficiency. In our population the mean age of ESRD onset was 39 ± 10 years, with half of all surviving patients developing ESRD by age 47. This is consistent with an earlier report by Colombi et al ([11]) that the mean age of uremic death in Fabry patients in the predialysis era was 41 years. The average age at ESRD onset was reported as 35 years ([14]), 38 years ([38]), and 43 years ([29]). A recent analysis of United States Renal Data System data for the period 1995–1998 indicates that the mean age at which Fabry patients developed ESRD was 42 years (Abbott K, personal communication).

We found that once CRI developed, estimated GFR declined at −12.2 mL/min per year. By comparison, the rate of decline in renal function for diabetic patients with established nephropathy in the preangiotensin antagonist era ranged from −9 mL/min per year to −14 mL/min per year ([35,42,48,59]). A more recent study suggests that with aggressive hypertension control including the use of angiotensin converting enzyme inhibitors, the overall rate of progression in type I diabetic patients may be reduced to −4 mL/min per year ([23]). The functional decline in Fabry patients was substantially greater than that seen in patients with nondiabetic glomerular, tubular, or cystic renal disease (−5 mL/min/1.73 m^2/yr) ([48]), and was largely homogeneous, with a single patient declining at a substantially faster rate than the others. This homogeneity is in contrast to the great variability seen in other renal diseases, including diabetic nephropathy ([59]).

It is important to consider possible progression promoters that might contribute to the rapid decline in renal function in Fabry patients we have observed. Poorly controlled systemic hypertension, hyperglycemia, hyperlipidemia, and heavy proteinuria are all associated with more rapid progression of renal failure in diabetic nephropathy and other renal diseases ([23,30,48,61]). These factors were present in relatively few patients with CRI in our study, suggesting that much of the renal functional decline may be a direct consequence of the metabolic defect and of glycolipid deposition. Why this decline should be so rapid when the metabolic defect is present throughout life is not entirely clear. One possible explanation, although it is speculative, is that the declining renal function is particularly related to microvascular disease with kidney, and that renal functional impairment only develops when a critical threshold for microvascular disease is reached. Specifically, glomerular hemodynamic compensation may maintain relatively normal GFR until the compensation is no longer effective and then renal function rapidly declines. Angiotensin antagonist therapy has been shown to reduce the rate of decline in renal function in chronic proteinuric renal diseases of diverse etiologies ([47]). Relatively few of our patients received these agents, and we cannot evaluate their efficacy in delaying the progression of Fabry renal disease.

ESRD developed in 23% of the patients in the present study; this represents a minimum estimate of ESRD prevalence in Fabry patients, as some patients in the present study may develop ESRD in the future. How well does this figure for ESRD prevalence agree with epidemiologic data? The United States Renal Data System database lists 86 patients with Fabry disease who reached ESRD during the period 1 January 1992 to 3 June 1997, representing a rate of approximately 16 patients per year (Abbott K, personal communication). It has been found that prevalence of Fabry disease in the predominantly Caucasian population of Australia is 1:117,000 males ([33]). Another estimate of prevalence is 1:40,000 males, although the population is not specified ([12]). These prevalence estimates suggest that approximately 1,000–3,500 men in the United States have Fabry disease. Extrapolating from the 23% minimum prevalence ESRD in our study group, this would suggest that at least 250–800 Fabry patients who are alive today will eventually develop ESRD. Assuming a 55-year average life span, then one would predict that 5–15 Fabry patients would reach ESRD each year. This estimate agrees fairly well with the observed rate.

The renal pathology of Fabry disease has been described by many authors ([6,7,9,10,19,22,41,50,54,62]). Classically, the glomeruli on light microscopy have enlarged glomerular visceral epithelial cells distended with foamy appearing vacuoles, mesangial widening, and varying degrees of glomerular obsolescence. Similar vacuolization may be seen in capillary endothelium and distal renal tubular cells. Sudan black stain demonstrates that the vacuoles contain lipid. On electron microscopy, concentrically lamellated osmiophilic inclusions are seen in the

cytoplasm of glomerular epithelial cells, and cells of the distal tubule and collecting duct. In the largest available renal biopsy study, Gubler et al ([22]) described pathologic findings in 12 patients, including 9 male patients (aged 11–29 years) and 3 female patients (aged 8–51 years). Four of the males and none of the females had developed proteinuria, but all except 1 22-year-old female had extensive lipid storage inclusions in glomerular podocytes, distal convoluted tubule, and endothelial cells. All males except the youngest had developed some tubular atrophy and interstitial fibrosis, but only the oldest female had tubulointerstitial atrophy and fibrosis.

The finding that renal Gb3 content, renal pathology, and renal function correlate with residual α-gal A activity in leukocytes suggests the possibility that residual α-gal A activity in kidney tissue retards the progression of Fabry renal disease. It remains to be determined whether α-gal A activity in kidney or other tissues correlates with residual α-gal A activity in peripheral blood leukocytes. It will be important to determine whether higher residual α-gal A in leukocytes also correlates with other clinical syndromes, particularly cerebrovascular and cardiovascular disease.

The role of renal transplantation in patients with Fabry disease has been the subject of several controversies. First, 2 groups described patients following renal transplantation whose serum contained increased α-gal A activity, and suggested that transplantation might ameliorate systemic manifestations ([13,44,45]). These data were soon challenged ([8]). More recent data suggest that following renal transplant plasma α-gal A activity is not increased, while urinary excretion of α-gal A rises to normal levels ([26,43,57]). Renal transplant has no detectable effect on the progression of involvement in nonrenal tissues ([8,20,21,43,57]).

Second, it was unclear whether recurrent Fabry disease would compromise allograft function. Renal tissue examined 6 months and 8 years following renal transplant showed Fabry inclusions in the vascular endothelium, demonstrable only by electron microscopy ([18,20]). This may represent colonization of the allograft vasculature by host endothelial cells ([31]). Development of osmiophilic inclusions in glomerular podocytes or tubular cells of renal allografts has rarely been reported ([21,36]). Third, the Fabry patients undergoing renal transplant were initially reported to have a 60% mortality rate at 1 year ([29]). Subsequently, it has been reported that renal and patient survival are comparable to that of patients with other renal diseases ([14,38]).

The clinical course of the transplanted patients in our series demonstrates that renal transplantation can provide long-term amelioration of uremia in Fabry patients, and that graft survival is comparable to that of patients with other etiologies of ESRD. The minimal effect of renal transplantation on extrarenal symptoms of Fabry disease is in keeping with the published experiences outlined above. It is clear that renal transplantation should be considered an effective therapy for ESRD in Fabry patients who are suitable renal transplant candidates. Clinically evident recurrence of Fabry renal disease was not noted, but we did not have an adequate number of renal transplant biopsies to evaluate the true frequency of histologic recurrence.

Altarescu et al ([1]) earlier found that α-gal A activity was lower in our Fabry patients with neuropathic pain compared to those who do not manifest neuropathic pain. Previous investigators have measured levels of α-gal A activity in individual patients, or multiple members of a kindred ([6,50]), or have tabulated the presence or absence of renal pathologic changes with enzyme level ([22]), but it has not been possible to correlate enzyme measurements with the long-term clinical course of Fabry renal disease or with renal pathologic findings on a larger scale.

We now report a protective effect of measurable residual α-gal A activity in delaying the onset of CRI by several years. Only a small amount of residual α-gal A activity is required to demonstrate an effect. Despite this temporary enhancement in renal survival however, our data suggest that all male Fabry patients who live long enough will eventually develop CRI and ESRD.

The results of the blinded scoring of baseline renal biopsies obtained from patients in a trial of enzyme replacement with recombinant α-gal A suggest that endogenous enzyme activity level influences the severity of renal histologic damage in patients of comparable age. While the histologic assessment of Gb3 inclusions in

tissue sections was not different between patients with undetectable and detectable residual α-gal A activity, quantitative analysis of Gb3 normalized to kidney weight indicates increased Gb3 content in renal tissue of patients with undetectable residual α-gal A activity. Other parameters, such as plasma Gb3 content, did not correlate with residual α-gal A activity. The reasons for this difference must remain speculative, but might indicate that tissues differ in the minimum threshold enzyme activity that is required to metabolize glycosphingolipid and that tissues with increased glycosphingolipid may require more α-gal A.

Studies of α-gal A mutations in Fabry disease have indicated that most mutations are unique, representing private mutations. At least 150 mutations have been identified ([3,16,37,39,55]). Other patients who lack mutations in the coding region have decreased α-gal A RNA in leukocytes, suggesting the possibility of additional defects in the transcriptional control regions ([37]). Our patients had 14 missense mutations and 20 mutations that resulted in deletion, insertions, or premature stop codons. The presence of a conservative substitution mutation predicts both a higher residual α-gal A level and a later onset of renal insufficiency compared to nonconservative mutations. A nonconservative change in amino acid or frameshift in the codon sequence could result in α-gal A with reduced or absent function and a less favorable renal disease course.

We found mutations in all exons of the α-gal A gene except exon 4. In our patients, nonconservative mutations in exons 3, 6, and 7 appeared to be associated with earlier progression to CRI, although the small number of patients precluded statistical analysis. Importantly, there was not an over-representation in these exons of nonconservative deletion, insertion, and premature stop codon mutations compared to nonconservative missense mutations, as the former might be expected to have a more deleterious effect on enzyme function. There is little structural information to allow the construction of a 3-dimensional model for α-gal A. Although these data are limited, we tentatively conclude that exons 3, 6, and 7 may encode amino acids that have particularly important roles at the active site of the enzyme or in serving other critical functions.

The degree of genotype/phenotype correlation in Fabry disease has been controversial. Thus within families, the same mutation may cause different phenotypes ([16]). In our patients, α-gal A activity was higher in patients with conservative mutations compared to those with nonconservative missense mutations. It has previously been reported that the prevalence of neuropathic pain was similar in patients with conservative missense mutations and nonconservative missense mutations ([1]). In the present study, we found that renal function was preserved longer in patients with conservative missense mutations compared to nonconservative missense mutations, and there was a similar trend in patients with conservative missense mutations compared to all other mutations. Thus, we have demonstrated a genotype/phenotype correlation for renal disease; the reason our findings differ from those of Eng and coworkers ([16]) may be the larger number of patients in our group and the quantitative approach.

The present paper has several limitations. First, not all patients were followed prospectively at the NIH from childhood; instead many were first seen as adults of different ages. Therefore, data were obtained by retrospective chart review, and not all types of data were available for all patients. Nonetheless, we obtained extensive medical records on many patients, extending back to the onset of medical care in many instances. Second, the patients were not randomly selected, as patients participated in NIH clinical studies following referral from physicians or as a result of self-referral. Nevertheless, the NIH studies of Fabry disease were not designed to examine renal manifestations. While we cannot exclude the possibility that the onset of renal disease would have provided motivation for patients to seek referral to the NIH, we believe that the prevalence and course of Fabry renal disease reported here are likely to be similar to those found in other patients. Third, our patients were almost exclusively Caucasian. While Fabry disease has been reported in all ethnic groups, it has been most commonly reported in patients of European or Asian origin. In general, the severity of Fabry disease has been reported to be similar in patients of different ethnic backgrounds, with the exception of a mutation showing a mild phenotype limited to cardiac pathology most often seen in Japan ([15,37]). Fourth, the study included only 5 patients with residual α-gal A levels >5%, of whom the highest was 12%. Therefore caution is warranted in predicting the severity of renal disease in patients with levels of α-gal A in this range. Fifth, the present report has examined only hemizygous male patients. The clinical course of female Fabry patients is known to be highly variable, due to random X chromosome inactivation in different tissues.

Our data suggesting that modestly higher levels of residual α-gal A activity are associated with enhanced renal survival may serve to strengthen the rationale for replacement therapy with recombinant α-gal A enzyme, which has already undergone clinical trials, or for gene therapy. Small increments in enzyme activity may be important in slowing the progression of renal disease. There are 2 important caveats to consider before instituting such therapies. First, it will have to be demonstrated that systemic administration of α-gal A can alter renal functional survival, presumably as a consequence of enzyme uptake by renal parenchymal cells. Second, no data have been published indicating whether cerebrovascular and cardiovascular disease, which are major causes of morbidity and death in these patients, are milder in patients with higher levels of residual α-gal A activity. In the present study, some patients with delayed onset of CRI nevertheless had disabling strokes or cardiovascular disease at an early age, and most had neuropathic pain for many years. However, the possibility that replacement therapy or gene therapy, instituted at an early age, might retard substrate accumulation and preserve long-term renal function should be explored. Demonstration of therapeutic efficacy will require appropriate placebo controls, but additional evidence may be derived from a finding that the course of renal disease is favorably altered compared to the natural history described here.

Summary

We reviewed the medical records of 105 male patients with Fabry disease. We describe the clinical course and histology of their renal disease and correlate them with residual α-galactosidase A (α-gal A) activity and with mutations in the α-gal A gene. Hemizygous male patients with Fabry disease may develop proteinuria and chronic renal insufficiency in adolescence or early adulthood. By age 35 years, 50% of patients had non-nephrotic range proteinuria and almost 20% had early renal insufficiency. Fifty percent of surviving patients had renal insufficiency by age 42 years, and 50% had progressed to end-stage renal disease by age 47 years. Twenty-three percent of all patients eventually developed end-stage renal disease. By age 55 years, 50% of the patients had died, and all had died by age 60 years. Nephrotic proteinuria was present in 18% of patients and hypertension was present in 30% of patients. Either manifestation may appear before or after the onset of chronic renal insufficiency. After the onset of chronic renal insufficiency, the mean rate of change in glomerular filtration rate was -12.2 mL/min per year with patients reaching end-stage renal disease after 4.1 years. The presence of detectable residual α-gal A activity in peripheral leukocytes was associated with a later onset of chronic renal insufficiency, lower renal globotriaosylceramide content, and lower scores for renal histologic damage. Conservative missense mutations were associated with longer renal survival compared with nonconservative missense or other mutations.

Acknowledgments

The authors thank Connie Kreps, RN, for assistance with chart reviews, Ellen Vaughan, RN, for performing inulin clearances, David C. Smith, CRNP, for obtaining death certificates, Ashwini Chavan, MD, for assistance with the renal pathology analysis, Neal Jeffries, PhD, and Robert Wesley, PhD, for statistical advice, and Kevin Abbott, MD, for sharing unpublished data.

References

1. Altarescu GM, Goldfarb LG, Park K-Y, Kaneski C, Jeffries N, Litvak S, Nagle JW, Schiffmann R. Identification of fifteen novel mutations and genotype-phenotype relationship in Fabry disease. Clin Genet 60: 46–51, 2001.

- Cited Here

2. Anderson W. A case of “angiokeratoma”. Br J Dermatol 10: 113–7, 1898.

- Cited Here

3. Ashton-Prolla P, Tong B, Shabbeer J, Astrin KH, Eng CM, Desnick RJ. Fabry disease: Twenty-two novel mutations in the alpha-galactosidase A gene and genotype/phenotype correlations in severely and mildly affected hemizygotes and heterozygotes. J Invest Med 48: 227–35, 2000.

- Cited Here

4. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med 276: 1163–7, 1967.

- Cited Here

5. Brady RO, Tallman JF, Johnson WG, Gal AE, Leahy WR, Quirk JM, Dekaban AS. Replacement therapy for inherited enzyme deficiency. Use of purified ceramidetrihexosidase in Fabry's disease. N Engl J Med 289: 9–14, 1973.

6. Burkholder PM, Updike SJ, Ware RA, Reese OG. Clinicopathologic, enzymatic, and genetic features in a case of Fabry's disease. Arch Pathol Lab Med 104: 17–25, 1980.

- Cited Here

7. Chen HC, Tsai JH, Lai YH, Guh JY. Renal changes in heterozygous Fabry's disease—a family study. Am J Kidney Dis 15: 180–3, 1990.

- Cited Here

8. Clarke JT, Guttmann RD, Wolfe LS, Beaudoin JG, Morehouse DD. Enzyme replacement therapy by renal allotransplantation in Fabry's disease. N Engl J Med 287: 1215–8, 1972.

- Cited Here

9. Cohen AH. Renal pathology forum. Am J Nephrol 5: 305–11, 1985.

- Cited Here

10. Colley J, Miller D, Hutt M, Wallace H. The renal lesion in angiokeratoma corporis diffusum. Br Med J 1: 1266–8, 1958.

- Cited Here

11. Colombi A, Kostyal A, Bracher R, Gloor F, Mazzi R, Tholen H. Angiokeratoma corporis diffusum—Fabry's disease. Helv Med Acta 34: 67–83, 1967.

- Cited Here

12. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Valle D, ed. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw Hill, pp 2741–84, 2000.

- Cited Here

13. Desnick RJ, Simmons RL, Allen KY, Woods JE, Anderson CF, Najarian JS, Krivit W. Correction of enzymatic deficiencies by renal transplantation: Fabry's disease. Surgery 72: 203–11, 1972.

- Cited Here

14. Donati D, Novario R, Gastaldi L. Natural history and treatment of uremia secondary to Fabry's disease: An European experience. Nephron 46: 353–9, 1987.

- Cited Here

15. Eng CM, Desnick RJ. Molecular basis of Fabry disease: Mutations and polymorphisms in the human alpha-galactosidase A gene. Hum Mutat 3: 103–11, 1994.

- Cited Here

16. Eng CM, Niehaus DJ, Enriquez AL, Burgert TS, Ludman MD, Desnick RJ. Fabry disease: Twenty-three mutations including sense and antisense CpG alterations and identification of a deletional hot-spot in the alpha-galactosidase A gene. Hum Mol Genet 3: 1795–9, 1994.

- Cited Here

17. Fabry J. Ein Beitrag zur Kenntnis der Purpura haemorrhagica nodularis. Arch Dermatol Syphilol 43: 187–200, 1898.

- Cited Here

18. Faraggiana T, Churg J, Grishman E, Strauss L, Prado A, Bishop DF, Schuchman E, Desnick RJ. Light- and electron-microscopic histochemistry of Fabry's disease. Am J Pathol 103: 247–62, 1981.

- Cited Here

19. Farge D, Nadler S, Wolfe LS, Barre P, Jothy S. Diagnostic value of kidney biopsy in heterozygous Fabry's disease. Arch Pathol Lab Med 109: 85–8, 1985.

- Cited Here

20. Friedlaender MM, Kopolovic J, Rubinger D, Silver J, Drukker A, Ben-Gershon Z, Durst AL, Popovtzer MM. Renal biopsy in Fabry's disease eight years after successful renal transplantation. Clin Nephrol 27: 206–11, 1987.

- Cited Here

21. Gantenbein H, Bruder E, Burger HR, Briner J, Binswanger U. Recurrence of Fabry's disease in a renal allograft 14 years after transplantation. Nephrol Dial Transplant 10: 287–9, 1995.

- Cited Here

22. Gubler MC, Lenoir G, Grunfeld JP, Ulmann A, Droz D, Habib R. Early renal changes in hemizygous and heterozygous patients with Fabry's disease. Kidney Int 13: 223–35, 1978.

- Cited Here

23. Hovind P, Rossing P, Tarnow L, Smidt UM, Parving HH. Progression of diabetic nephropathy. Kidney Int 59: 702–9, 2001.

- Cited Here

24. Hozumi I, Nishizawa M, Ariga T, Miyatake T. Biochemical and clinical analysis of accumulated glycolipids in symptomatic heterozygotes of angiokeratoma corporis diffusum (Fabry's disease) in comparison with hemizygotes. J Lipid Res 31: 335–40, 1990.

25. Ko YH, Kim HJ, Roh YS, Park CK, Kwon CK, Park MH. Atypical Fabry's disease. An oligosymptomatic variant. Arch Pathol Lab Med 120: 86–9, 1996.

- Cited Here

26. Krivit W, Bernlohr RW, Desnick RJ. Enzyme replacement in genetic disease. Prospectus. Birth Defects Orig Artic Ser 9: 232–3, 1973.

- Cited Here

27. Kusiak JW, Quirk JM, Brady RO. Purification and properties of the two major isozymes of alpha-galactosidase from human placenta. J Biol Chem 253: 184–90, 1978.

- Cited Here

28. Lee GR. Wintrobe's clinical hematology. 10th ed. Baltimore: Lippincott Williams & Wilkins, p 777, 1999.

- Cited Here

28a. Levey AS, Greene T, Kusek JW, Beck GJ, MDRD Study Group. A simplified equation to predict glomerular filtration rate. J Am Soc Nephrol 11: 155A, 2000.

- Cited Here

29. Maizel SE, Simmons RL, Kjellstrand C, Fryd DS. Ten-year experience in renal transplantation for Fabry's disease. Transplant Proc 13: 57–9, 1981.

- Cited Here

30. Marcantoni C, Ortalda V, Lupo A, Maschio G. Progression of renal failure in diabetic nephropathy. Nephrol Dial Transplant 13(Suppl 8): 16–9, 1998.

- Cited Here

31. McMahon J, Tubbs DO, Gephardt G, Steinmuller D. Pseudo-reoccurrence of Fabry's disease in renal allograft [abstract]. Lab Invest 54: 42A, 1986.

- Cited Here

32. McNary W, Lowenstein L. A morphological study of the renal lesion in angiokeratoma corporis diffusum universale (Fabry's disease). J Urol 93: 641–8, 1965.

- Cited Here

33. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 281: 249–54, 1999.

- Cited Here

34. Meroni M, Sessa A, Battini G, Tazzari S, Torri Tarelli L. Kidney involvement in Anderson-Fabry disease. Contrib Nephrol 122: 178–84, 1997.

- Cited Here

35. Mogensen CE. Progression of nephropathy in long-term diabetics with proteinuria and effect of initial anti-hypertensive treatment. Scand J Clin Lab Invest 36: 383–8, 1976.

- Cited Here

36. Mosnier JF, Degott C, Bedrossian J, Molas G, Degos F, Pruna A, Potet F. Recurrence of Fabry's disease in a renal allograft eleven years after successful renal transplantation. Transplantation 51: 759–62, 1991.

- Cited Here

37. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, Yoshida A, Kuriyama M, Hayashibe H, Sakuraba H, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med 333: 288–93, 1995.

- Cited Here

38. Ojo A, Meier-Kriesche HU, Friedman G, Hanson J, Cibrik D, Leichtman A, Kaplan B. Excellent outcome of renal transplantation in patients with Fabry's disease. Transplantation 69: 2337–9, 2000.

- Cited Here

39. Okumiya T, Kawamura O, Itoh K, Kase R, Ishii S, Kamei S, Sakuraba H. Novel missense mutation (M72V) of alpha-galactosidase gene and its expression product in an atypical Fabry hemizygote. Hum Mutat (Suppl 1): S213–6, 1998.

- Cited Here

40. Orimo S, Iwasaki T, Yoshino H, Arai M, Hiyamuta E. An autopsied case of Fabry's disease presenting with parkinsonism and cardiomegaly as a cardinal clinical manifestation. Rinsho Shinkeigaku 34: 1003–7, 1994.

- Cited Here

41. Pabico RC, Atancio BC, McKenna BA, Pamukcoglu T, Yodaiken R. Renal pathologic lesions and functional alterations in a man with Fabry's disease. Am J Med 55: 415–25, 1973.

- Cited Here

42. Parving HH, Smidt UM, Friisberg B, Bonnevie-Nielsen V, Andersen AR. A prospective study of glomerular filtration rate and arterial blood pressure in insulin-dependent diabetics with diabetic nephropathy. Diabetologia 20: 457–61, 1981.

- Cited Here

43. Peces R. Is there true recurrence of Fabry's disease in the transplanted kidney? Nephrol Dial Transplant 11: 561, 1996.

- Cited Here

44. Philippart M, Franklin SS, Gordon A. Reversal of an inborn sphingolipidosis (Fabry's disease) by kidney transplantation. Ann Intern Med 77: 195–200, 1972.

- Cited Here

45. Philippart M, Franklin SS, Leeber DA, Hull AR, Peters PC. Kidney transplantation in Fabry's disease. N Engl J Med 289: 270–1, 1973.

- Cited Here

46. Praga M, Borstein B, Andres A, Arenas J, Oliet A, Montoyo C, Ruilope LM, Rodicio JL. Nephrotic proteinuria without hypoalbuminemia: Clinical characteristics and response to angiotensin-converting enzyme inhibition. Am J Kidney Dis 17: 330–8, 1991.

- Cited Here

47. Ruggenenti P, Pagano E, Tammuzzo L, Benini R, Garattini L, Remuzzi G. Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. Kidney Int 59 (1): 286–94., 2001.

- Cited Here

48. Ruggenenti P, Perna A, Gherardi G, Benini R, Remuzzi G. Chronic proteinuric nephropathies: Outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. Am J Kidney Dis 35: 1155–65, 2000.

- Cited Here

49. Sakuraba H, Yanagawa Y, Igarashi T, Suzuki Y, Suzuki T, Watanabe K, Ieki K, Shimoda K, Yamanaka T. Cardiovascular manifestations in Fabry's disease. A high incidence of mitral valve prolapse in hemizygotes and heterozygotes. Clin Genet 29: 276–83, 1986.

- Cited Here

50. Savi M, Olivetti G, Neri TM, Curtoni C. Clinical, histopathological, and biochemical findings in Fabry's disease. A case report and family study. Arch Pathol Lab Med 101: 536–9, 1977.

- Cited Here

51. Schiffmann R, Kopp JB, Austin 3rd, HA Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in fabry disease: A randomized controlled trial. JAMA 285: 2743–9, 2001.

- Cited Here

52. Schiffmann R, Murray GJ, Treco D, Daniel P, Sellos-Moura M, Myers M, Quirk JM, Zirzow GC, Borowski M, Loveday K, Anderson T, Gillespie F, Oliver KL, Jeffries NO, Doo E, Liang TJ, Kreps C, Gunter K, Frei K, Crutchfield K, Selden RF, Brady RO. Infusion of alpha-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. Proc Natl Acad Sci U S A 97: 365–70, 2000.

- Cited Here

53. Sheps SG. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 157: 2413–46, 1997.

- Cited Here

54. Sirvent AE, Enriquez R, Antolin A, Cabezuelo JB, Teruel A, Rodriguez Ledesma JM, Gonzalez C, Reyes A. Fabry's disease presenting with oligoanuric end-stage renal failure. Nephrol Dial Transplant 12: 1503–5, 1997.

- Cited Here

55. Topaloglu AK, Ashley GA, Tong B, Shabbeer J, Astrin KH, Eng CM, Desnick RJ. Twenty novel mutations in the alpha-galactosidase A gene causing Fabry disease. Mol Med 5: 806–11, 1999.

- Cited Here

56. Tubbs RR, Gephardt GN, McMahon JT, Hall PM, Gifford RW. Cytoplasmic inclusions of Fabry's disease. Ultrastructural demonstration of their presence in urine sediment. Arch Pathol Lab Med 105: 361–2, 1981.

- Cited Here

57. Van den Bergh FA, Rietra PJ, Kolk-Vegter AJ, Bosch E, Tager JM. Therapeutic implications of renal transplantation in a patient with Fabry's disease. Acta Med Scand 200: 249–56, 1976.

- Cited Here

58. Vance DE, Krivit W, Sweeley CC. Concentrations of glycosyl ceramides in plasma and red cells in Fabry's disease, a glycolipid lipidosis. J Lipid Res 10: 188–92, 1969.

59. Viberti GC, Bilous RW, Mackintosh D, Keen H. Monitoring glomerular function in diabetic nephropathy. A prospective study. Am J Med 74: 256–64, 1983.

- Cited Here

60. von Scheidt W, Eng CM, Fitzmaurice TF, Erdmann E, Hubner G, Olsen EG, Christomanou H, Kandolf R, Bishop DF, Desnick RJ. An atypical variant of Fabry's disease with manifestations confined to the myocardium. N Engl J Med 324: 395–9, 1991.

- Cited Here

61. Yokoyama H, Tomonaga O, Hirayama M, Ishii A, Takeda M, Babazono T, Ujihara U, Takahashi C, Omori Y. Predictors of the progression of diabetic nephropathy and the beneficial effect of angiotensin-converting enzyme inhibitors in NIDDM patients. Diabetologia 40: 405–11, 1997.

- Cited Here

62. Yuen NW, Lam CW, Chow TC, Chiu MC. A characteristic dissection microscopy appearance of a renal biopsy of a Fabry heterozygote. Nephron 77: 354–6, 1997.

- Cited Here

View full references list

Cited By

This article has been cited **8** time(s).

Genetics in Medicine
Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry
Waldek, S; Patel, MR; Banikazemi, M; Lemay, R; Lee, P
Genetics in Medicine, 11(11): 790-796.
10.1097/GIM.0b013e3181bb05bb
PDF (286) | CrossRef
Genetics in Medicine
A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease
Whybra, C; Miebach, E; Mengel, E; Gal, A; Baron, K; Beck, M; Kampmann, C
Genetics in Medicine, 11(6): 441-449.
10.1097/GIM.0b013e3181a23bec
PDF (883) | CrossRef
Genetics in Medicine
The pharmacology of multiple regimens of agalsidase alfa enzyme replacement therapy for Fabry disease
Clarke, JT; West, ML; Bultas, J; Schiffmann, R
Genetics in Medicine, 9(8): 504-509.
10.1097/GIM.0b013e318133fb1b
PDF (582) | CrossRef
Genetics in Medicine
Quantitative dysmorphology assessment in Fabry disease
Ries, M; Moore, DF; Robinson, CJ; Tifft, CJ; Rosenbaum, KN; Brady, RO; Schiffmann, R; Krasnewich, D

Genetics in Medicine, 8(2): 96-101.
10.1097/01.gim.0000200950.25118.dd
PDF (1396) | CrossRef
Medicine
The Relationship of Vascular Glycolipid Storage to Clinical Manifestations of Fabry Disease: A Cross-Sectional Study of a Large Cohort of Clinically Affected Heterozygous Women
Gupta, S; Ries, M; Kotsopoulos, S; Schiffmann, R
Medicine, 84(5): 261-268.
10.1097/01.md.0000178976.62537.6b
PDF (179) | CrossRef
Genetics in Medicine
Fabry disease: Guidelines for the evaluation and management of multi-organ system involvement
Eng, CM; Germain, DP; Banikazemi, M; Warnock, DG; Wanner, C; Hopkin, RJ; Bultas, J; Lee, P; Sims, K; Brodie, SE; Pastores, GM; Strotmann, JM; Wilcox, WR
Genetics in Medicine, 8(9): 539-548.
10.1097/01.gim.0000237866.70357.c6
PDF (302) | CrossRef
Genetics in Medicine
Comparative evaluation of [alpha]-galactosidase A infusions for treatment of Fabry disease
Hopkin, RJ; Bissler, J; Grabowski, aA
Genetics in Medicine, 5(3): 144-153.

PDF (1325)
Genetics in Medicine
Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life
Wang, RY; Lelis, A; Mirocha, J; Wilcox, WR
Genetics in Medicine, 9(1): 34-45.
10.1097/GIM.0b013e31802d8321
PDF (842) | CrossRef

View full article text

Related Articles

- **IgA nephropathy with mimicking Fabry disease: A case report and literature review**
- **Case report and literature review: Fabry disease misdiagnosing as polymyalgia rheumatica**
- **Coexistence of Fabry disease with IgM nephropathy**
- **Fabry disease with early-onset ventricular dilation**
- **Fabry disease and immunoglobulin A nephropathy presenting with Alport syndrome-like findings**
- **A phase II, multicenter, open-label trial to evaluate the safety and efficacy of ISU303 (Agalsidase beta) in patients with Fabry disease**

Most Popular

- [Citizens protein project: A self-funded, transparent, and concerning report on analysis of popular protein supplements sold in the Indian market]
- [An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract]
- [Higher volume of water intake is associated with lower risk of albuminuria and chronic kidney disease]
- [Breast cancer: A review of risk factors and diagnosis]
- [Suicide attempt using sodium nitrite ordered on the internet: Two case reports]

^Back to Top

Never Miss an Issue

Get new journal Tables of Contents sent right to your email inbox Type your email
Get New Issue Alerts

Browse Journal Content

- Most Popular
- For Authors
- About the Journal
- Past Issues
- Current Issue
- Register on the website
- Get eTOC Alerts

For Journal Authors

- Submit an article
- How to publish with us

Customer Service

Live Chat

- Browse the help center
- Help
- Contact us at:
  - Support:
    Submit a Service Request
  - TEL: (USA):
    TEL: (Int'l):
    800-638-3030 (within USA)
    301-223-2300 (international)