

Coronary Artery and Other Vascular Calcifications in Patients with Cystinosis after Kidney Transplantation

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Cystinosis, an autosomal recessive disorder of lysosomal cystine accumulation, results from mutations in the *CTNS* gene that encodes the lysosomal cystine transporter, cystinosin. Renal tubular Fanconi syndrome occurs in infancy, followed by rickets, growth retardation, photophobia, and renal failure, which requires renal transplantation at approximately 10 yr of age. Treatment with cysteamine decreases cellular cystine levels, retards renal deterioration, and allows for normal growth. Patients with a history of inadequate cystine depletion therapy may survive, after renal transplantation, into the third to fifth decades but will experience other, extrarenal complications of the disease. Routine chest and head computed tomography scans of 41 posttransplantation patients with cystinosis were reviewed for vascular calcification. The radiologic procedures had been performed to examine lung and brain parenchyma, so there was little ascertainment bias. Thirteen of the 41 patients had vascular calcification, including 11 with coronary artery calcification. One 25-yr-old man required three-vessel coronary artery bypass graft surgery. There were no significant differences between the 13 patients with calcification and the 28 without calcification in the following parameters: Time on dialysis, frequency of transplantation, hypertension, hypercholesterolemia, homozygosity for the 57-kb deletion in *CTNS*, serum creatinine, and calcium-phosphate product. However, the finding of vascular calcification correlated directly with duration of life without cysteamine therapy and inversely with duration of life under good cystine-depleting therapy. The accumulation of intracellular cystine itself maybe a risk factor for vascular calcifications, and older patients with cystinosis should be screened for this complication.

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Cystinosis is an autosomal recessive lysosomal storage disease with an estimated incidence of one in 100,000 to 200,000 live births (1,2). *CTNS*, the gene that is responsible for cystinosis, maps to chromosome 17p13 (3) and encodes a lysosomal membrane transport protein named cystinosin (4). Approximately half of patients who have cystinosis and are of northern European descent carry at least one allele that bears a specific 57-kb deletion that encompasses the *CTNS* gene (4,5). For all patients with nephropathic cystinosis, a defect in cystinosin dramatically diminishes egress of cystine from lysosomes (6,7), resulting in intralysosomal cystine accumulation and crystal formation in most organ systems (1,2). Infants with cystinosis are normal at birth but develop renal tubular Fanconi syndrome at 6 to 12 mo of age and renal failure at approximately 10 yr of age (8). In addition, hypothyroidism (1,2), myopathy (9,10), swallowing dysfunction (11), diabetes (12), male hypogonadism (13), pulmonary dysfunction (14),

and central nervous system involvement (15–17) complicate this disorder in adolescence and early adulthood (18).

The therapy of nephropathic cystinosis includes replacement of the mineral and electrolyte losses associated with the renal tubular Fanconi syndrome. When glomerular failure supervenes, dialysis or kidney transplantation is required. In addition, specific therapy directed at intracellular cystine depletion involves administration of oral cysteamine bitartrate, or Cystagon (Mylan Pharmaceuticals, Morgantown, WV) (19). Chronic use of oral cysteamine, now accepted as the treatment of choice for cystinosis throughout the world, retards renal glomerular deterioration (20,21), enhances growth, and obviates the need for L-thyroxine replacement in patients with cystinosis (22). Cysteamine hydrochloride eyedrops also dissolve the corneal crystals of cystinosis (23,24).

Increasing numbers of individuals with cystinosis are receiving renal transplants and living into adulthood, and more late complications of the disease and its treatments are being recognized. As part of our comprehensive evaluations of adult patients with cystinosis after renal transplantation, we performed head and chest computed tomography (CT) studies, which revealed calcification in various vessels, most notable the coronary arteries. We now present these findings as a complication of nephropathic cystinosis after renal

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transplantation in patients with a history of inadequate oral cysteamine therapy.

Materials and Methods

Patients

Nephropathic cystinosis was diagnosed on the basis of characteristic clinical findings plus an elevated leukocyte cystine content: >3.0 nmol half-cystine/mg protein (normal <0.2). All patients were enrolled in a protocol that was approved by the Institutional Review Boards of the National Institute of Child Health and Human Development and the National Human Genome Research Institute, and all patients gave written informed consent. Cystinosis severity scores (5) were based on age at diagnosis, the Fanconi Syndrome Index (a measure of aminoaciduria [25]), pretreatment leukocyte cystine levels (measured using the cystine binding protein assay [26]), age at renal failure, and age at which serious extrarenal complications occurred (27).

Radiologic Procedures

All of the CT studies were obtained according to standard clinical protocols for the head and the body. For the brain studies, the earliest two were obtained on spiral CT equipment (General Electric Medical Systems, Milwaukee, WI). All subsequent brain studies were conducted using multichannel ("multislice") machines (Philips Medical Systems, Eindhoven, Netherlands; and General Electric Medical Systems). All studies used 5-mm or thinner collimation. For the torso studies, the earliest three were performed on spiral CT equipment, using either 5- or 10-mm collimation and 1:1 pitch; all subsequent chest studies were obtained using these same multichannel scanners and consecutive 5-mm images. Both head and chest studies were conducted without vascular contrast administration.

Molecular Diagnostics

Mutation analysis of the *CTNS* gene, using multiplex analysis of the 57-kb deletion, was performed as described (5,28).

Results

Between October 1997 and January 2005, 41 patients who were aged 8 to 47 and had nephropathic cystinosis underwent a CT scan of the chest to rule out parenchymal lung disease. When multiple CT scans were available on a patient, only the most recent result was included in this analysis. Thirteen (32%) patients had vascular calcification detected incidentally; in 11, the calcification was in the coronary arteries. The characteristics of the 13 patients with calcifications were compared with those of 28 patients who lacked vascular calcifications (Table 1). The 13 patients with vascular calcifications were older ($P = 1 \times 10^{-7}$) and had lived longer without cysteamine therapy than the 28 patients who lacked vascular calcifications ($P = 3 \times 10^{-6}$). The duration of treatment with oral cysteamine therapy was shorter for the group with vascular calcifications than for the group without this complication, although the difference did not approach statistical significance ($P = 0.21$). When all 41 patients were considered, the fraction with vascular calcifications increased with the number of years off cysteamine (Figure 1A) and decreased with the number of years on cysteamine (Figure 1B). The groups with and without vascular calcifications differed significantly in the frequency of diabetes ($P = 0.0034$); all of the patients who required insulin had undergone a renal allograft procedure, were receiving prednisone, and had their diabetes for between 4 and 11 yr at the time of the CT examination. The groups with and without calcifications did not differ significantly in the duration of dialysis ($P = 0.06$) or in the fraction of patients who had received a renal allograft ($P = 0.07$). The two groups resembled each other in the frequency of hypertension, hypercholesterolemia, and homozygosity for the 57-kb deletion in *CTNS* (Table 1). They did not

Table 1. Characteristics of patients who had cystinosis with and without vascular calcifications

	No Calcifications <i>n</i> = 28 $\bar{x} \pm \text{SEM}$ (range)	Calcifications <i>n</i> = 13 $\bar{x} \pm \text{SEM}$ (range)	<i>P</i> ^a
Age (yr)	22.0 \pm 1.1 (8 to 33)	35.6 \pm 1.9 (24 to 47)	1×10^{-7}
Time off cysteamine (yr) ^b	14.3 \pm 1.8 (1 to 31)	30.9 \pm 2.3 (18 to 47)	3×10^{-6}
Time on cysteamine (yr)	7.8 \pm 1.5 (0 to 24)	4.7 \pm 1.3 (0 to 14)	0.21
Time on dialysis (yr)	0.7 \pm 0.3 (0 to 5) ^c	2.1 \pm 0.8 (0 to 11)	0.06
Diabetes (<i>n</i> patients)	2/28	6/13	0.0034
Posttransplantation (<i>n</i> patients)	22/28	13/13	0.07
Hypertensive ^d (<i>n</i> patients)	6/28	3/13	0.91
Homozygous 57-kb deletion ^e (<i>n</i> patients)	8/25	6/13	0.39
Hypercholesterolemia ^f (<i>n</i> patients)	7/28	4/13	0.70
Serum creatinine (mg/dl) ^g	1.6 \pm 0.2 (0.3 to 4.8)	1.9 \pm 0.4 (0.4 to 5.6)	0.59
Ca \times P product	40.8 \pm 2.3 (29 to 92)	38.0 \pm 2.4 (29 to 58)	0.47

^aT test (two-sided) or χ^2 test.

^bTo be considered to be receiving cysteamine adequately for any length of time, a leukocyte cystine value <2.5 nmol half-cystine/mg protein was required.

^c*n* = 27.

^dSystolic BP \geq 140 mmHg or diastolic BP \geq 90 mmHg.

^eIn *CTNS* gene; not all patients provided DNA for testing.

^fTotal cholesterol \geq 200 mg/dl or receiving lipid-lowering therapy.

^gDoes not include data of patients on dialysis (three with no calcifications; one with calcifications).

differ in mean serum creatinine concentration or calcium-phosphate product (Table 1). The posttransplantation patients took a wide variety of immunosuppressive agents but did not commonly receive lipid-lowering agents.

The clinical characteristics of the patients with vascular calcification are shown in Table 2. Twenty-three renal allografts had been performed on the 13 patients, nine of whom had undergone dialysis before the procedure. In addition to the three patients with total cholesterol levels >200 mg/dl (Tables 1 and 2), three other patients had triglyceride levels >150 mg/dl and one patient with diabetes had an LDL cholesterol level >100 mg/dl. All of these values constitute cardiovascular disease risk factors according to the National Cholesterol Education Program Adult Treatment Plan III guidelines.

Overall, the calcification involved various vessels, including the aorta, coronary, left subclavian, right brachiocephalic, carotid, and vertebral arteries. For example, extensive vertebral artery calcification was visible on CT scan of the head in patient 6 (Figure 2). The following cases illustrate the potential end-organ ischemic complications that can occur in posttransplantation patients with cystinosis and vascular calcification.

Patient 2 (Table 2) was a 25-yr-old Hispanic man who presented with symptoms of exercise-induced angina. He was born after an uncomplicated pregnancy but developed failure to thrive at 6 mo of age. At 1 yr of age, renal Fanconi syndrome and rickets were diagnosed. A definitive diagnosis of cystinosis was not made until 5 yr of age. The patient began hemodialysis at 7.5 yr of age and within 6 mo received a cadaveric renal allograft. He developed hypertension at age 10, hypothyroidism 1 yr later, and hypercholesterolemia during adolescence. Chronic graft rejection required a second, living-related donor transplant at 20 yr of age.

This patient's severity score was 2.7, reflecting a significant degree of impairment as a result of nephropathic cystinosis (5). His leukocyte cystine level, without cystine-depleting therapy, was 10.8 nmol half-cystine/mg protein (normal <0.2). Cysteamine therapy, in the form of phosphocysteamine, was initiated upon the patient's first admission to the National Institutes of Health (NIH) Clinical Center at 11 yr of age. Later, cysteamine bitartrate (Cystagon) was administered. The patient received cysteamine therapy between the ages of 10 and 15 yr, during which time his leukocyte cystine level averaged 2.2 nmol half-cystine/mg protein ($n = 8$; range 0.6 to 4.9) on doses ranging from 275 to 400 mg every 6 h. During this time, the leukocyte cystine was >2.5 nmol half-cystine/mg protein for a full year, meaning that compliant therapy was achieved for a total of 4 yr (Table 2). The patient did not return to the NIH for 10 yr, at which time he was 25 yr of age.

Recently, the patient complained of a "pressure-like" sensation while walking briskly or climbing stairs. He denied nausea, dyspnea, or radiation of the pressure or pain. He had never smoked. Further evaluation revealed hypothyroidism with a thyroid-stimulating hormone of 414 μ IU/ml (normal 0.40 to 4.00); free T_4 of 0.2 ng/dl (normal 0.7 to 1.8); and dyslipidemia with a total serum cholesterol of 233 mg/dl (normal 100 to 200 mg/dl), LDL of 163 mg/dl (normal 65 to 129), HDL of 37 mg/dl, and triglycerides of 200 mg/dl (normal <150). The

hemoglobin was 8.6 g/dl (normal 12.7 to 16.7), and the hematocrit was 25.2% (normal 36.7 to 48.3%), with a mean corpuscular volume of 91 fL (normal 79 to 98).

The resting 12-lead electrocardiogram showed marked sinus bradycardia with low voltage and nonspecific ST segment and T-wave abnormalities. A resting echocardiogram revealed no regional wall motion abnormalities or cardiomegaly. A routine chest CT, obtained as part of our pulmonary evaluation, showed marked calcification in the coronary arteries (Figure 3).

The patient underwent a combination dipyridamole and modified Bruce protocol treadmill stress test with thallium scintigraphy. The treadmill test was stopped after 4 min, 7 s (2.7 metabolic equivalents), because the patient complained of retrosternal chest pain and pressure, dyspnea, and pain radiating into his left arm. At peak exercise, the electrocardiogram showed 2-mm ST segment depression that resolved with rest. Thallium scintigraphy revealed a reversible perfusion defect in the inferior, apical, and septal segments of the myocardium. Subsequent cardiac catheterization (Figure 4) revealed several high-grade stenoses in the proximal left anterior descending artery, a 70% stenosis of the left circumflex before the first obtuse marginal branch, and 80% stenosis in the first obtuse marginal branch. There was also an almost 100% stenosis of the middle portion of the right coronary artery with left to right collaterals (data not shown). Coronary artery bypass was performed using both internal mammary arteries and one saphenous vein graft. Renal function remained stable throughout the hospitalization, with a creatinine clearance of 35 ml/min per

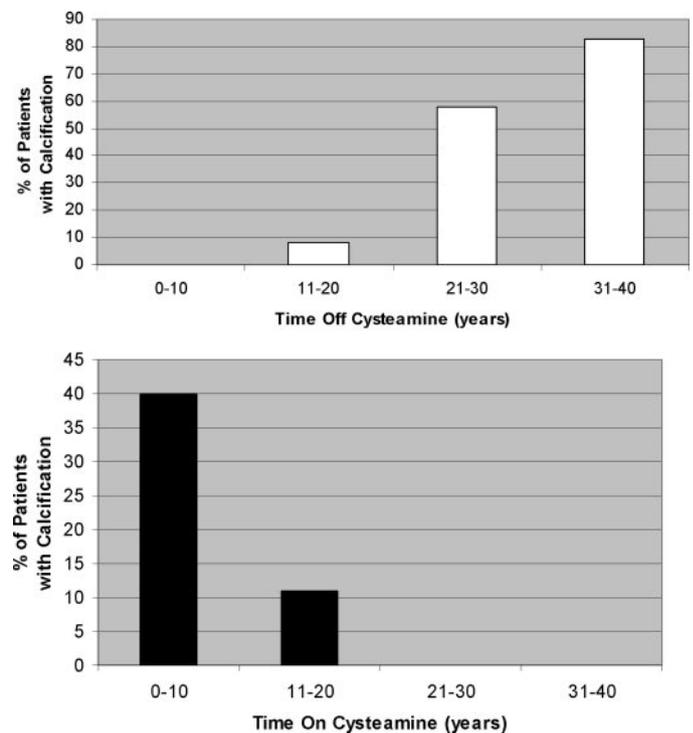


Figure 1. Percentage of patients who had cystinosis and vascular calcifications, divided according to the number of years off oral cysteamine therapy (A) or on cysteamine therapy (B).

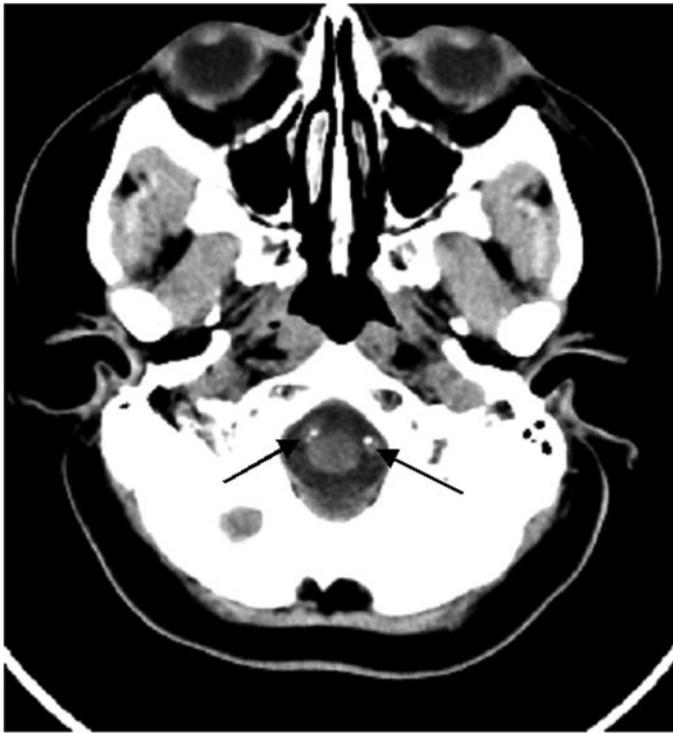


Figure 2. Vertebral artery calcifications on coronal computed tomography (CT) slice of patient 6. The black arrows highlight dense calcification of the vertebral arteries in this 33-yr-old man.

1.73 m². The patient was started on a β blocker, a statin, and low-dose aspirin and was discharged with follow-up care.

Patient 8 was a 37-yr-old white man with a history of three renal transplants and inadequate cysteamine treatment. He received a diagnosis of nephropathic cystinosis at age 13 mo and hypothyroidism at age 4 yr. Progressive chronic renal failure required hemodialysis and peritoneal dialysis for approximately 6 mo, followed by his first renal transplant at age 14. He received two additional renal allografts at ages 25 and 32 yr, after chronic graft rejection.

This patient had a cystinosis severity score of 1.8. He was homozygous for the 57-kb deletion in *CTNS*. The patient did not begin oral cysteamine therapy until age 20, and he tolerated 300 to 450 mg either three or four times per day over the next 17 yr. Leukocyte cystine levels from age 20 to 29 yr averaged 1.4 nmol half-cystine/mg protein (*n* = 9; range 0.5 to 2.7), but the patient did not return to the NIH between 29 and 37 yr of age. Hence, this patient is credited with 9 yr of “adequate” cysteamine therapy (Table 2).

The patient was hospitalized for a left-sided ischemic stroke at age 36. During that admission, he developed congestive heart failure as a result of volume overload and complained of substernal chest pain. Cardiac catheterization revealed a 75% lesion in his right coronary artery and a 40% lesion in the mid-left anterior descending coronary artery. The right coronary lesion was not amenable to percutaneous intervention, so medical management was initiated.

On routine admission to the NIH Clinical Center at age 37,

Table 2. Clinical features of patients with cystinosis and radiographic evidence of vascular calcifications^a

Patient	Age/ Gender	Age at Diagnosis (yr)	Age (yr) at Transplant 1st, 2nd, 3rd	Yr on Dialysis ^b	Yr off Cysteamine	Yr on Cysteamine	Serum Creatinine (mg/dl)	BP	Lipid Profile TC/TG/HDL/LDL (mg/dl)	<i>CTNS</i> 57-kb Deletion	Cardiovascular and Other Complications	Radiographic Locations of Vascular Calcifications
1	24/F	4	18	11	18	6	1.2	126/70	187/88/65/105	Homozygous	Diabetes; hypothyroidism, dysphagia	Left anterior descending and right coronary arteries
2	25/M	5	10, 19	3	21	4	1.4	120/76	233/200/37/163	None	Hypothyroidism, dyslipidemia	Extensive right and left coronary artery
3	29/F	1	16	3	28	1	1.0	93/55	244	Homozygous	Hypothyroidism, peritonitis	Abdominal aorta
4	33/M	5	10	2	32	1	7.3	200/117	119/52/59/42	Homozygous	Diabetes; hypothyroidism, renal failure, stroke	Left anterior descending, circumflex, and right coronary arteries
5	34/M	4	12, 20	0	26	8	0.4	112/74	171/163/52/89	None	Diabetes; hypothyroidism, dysphagia, seizure, sleep apnea, tinnitus	Right coronary and left subclavian arteries
6	34/M	0	8, 16	0	33	1	1.0	109/81	199/57/69/100	None	Diabetes; dysphagia, hypogonadism, muscular atrophy	Left anterior descending, right coronary, aorta, and vertebral arteries
7	35/F	1	8, 9, 22	0	28	7	2.7	168/103	111/233/24/46	Homozygous	Diabetes; hypothyroidism, seizure, hepatitis C, hearing loss	Left anterior descending and right coronary arteries
8	37/M	1	14, 25, 32	1	28	9	2.7	138/75	168/313/39/80	Homozygous	Hypothyroidism, stroke, dyslipidemia, hypogonadism, sleep apnea, heart failure, osteoporosis	Right coronary artery, right brachiocephalic artery, and carotid arteries
9	38/M	12	20	3	28	10	5.6	147/79	147/83/47/80	Heterozygous	Hypothyroidism, renal failure, dysphagia, muscle atrophy	Descending aorta
10	40/M	4	10, 18	0	40	0	1.3	128/78	142	Heterozygous	Diabetes; hypothyroidism, dysphagia, thoracic lordosis, parathyroidectomy	Left anterior descending and right coronary arteries
11	43/M	12	20	1	43	0	1.9	115/66	218/123/49/148	None	Hypothyroidism, dyslipidemia, seizure, skin cancer	Coronary arteries
12	44/M	0	10, 17	3	30	14	2.2	128/78	157/103/65/76	Homozygous	Hypothyroidism, diabetes, hypogonadism, keratopathy	Left anterior descending and circumflex arteries
13	47/F	24	30, 39	0	47	0	1.0	114/68	162/54/48/103	Heterozygous	Pseudotumor cerebri, mitral valve prolapse, dysmenorrhea	Left anterior descending artery and aorta

^aTC, total cholesterol; TG, triglycerides.

^bTo be considered to be receiving cysteamine adequately for any length of time, a leukocyte cystine value <2.5 nmol half-cystine/mg protein was required.

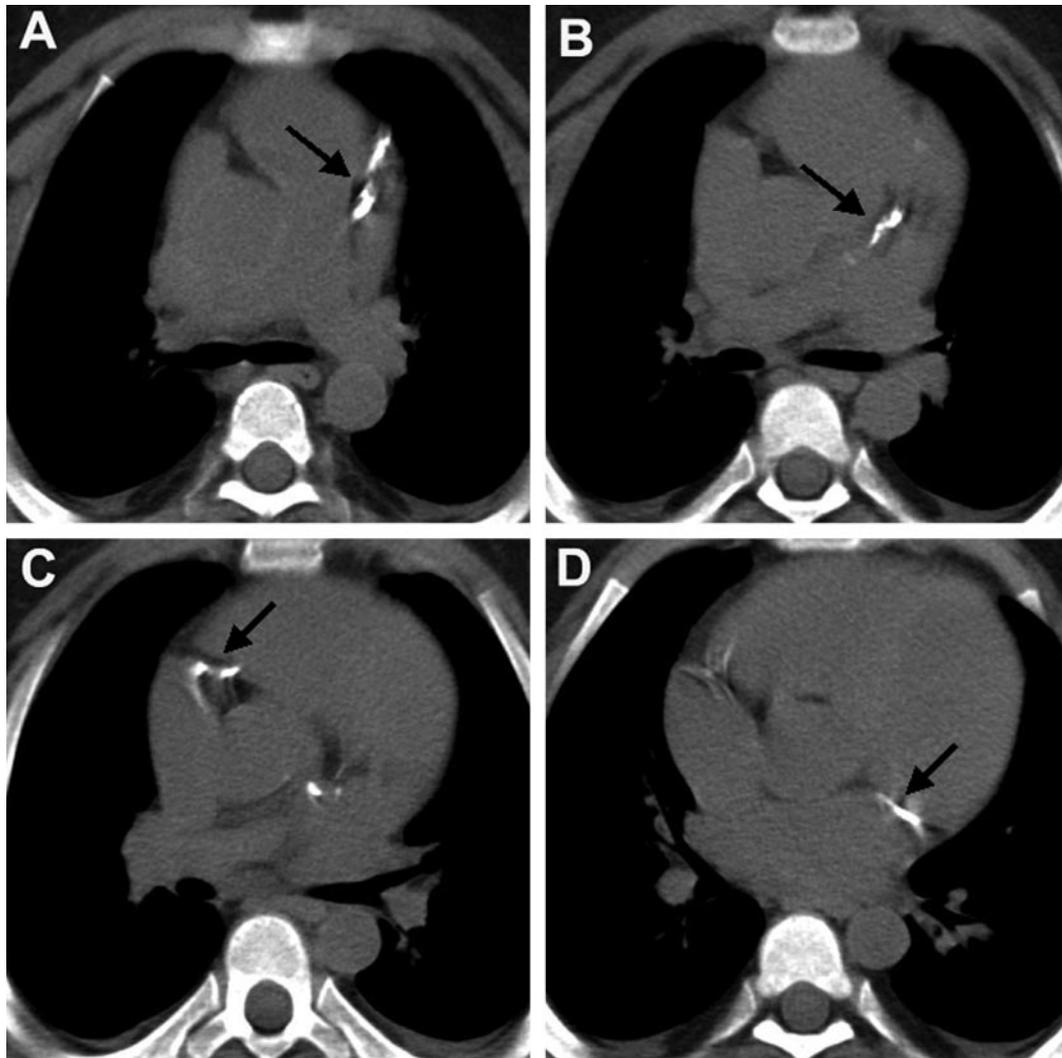


Figure 3. Chest CT of patient 2. (A and B) Dense calcification in the left anterior descending artery. (C) Calcification in the proximal portion of the right coronary artery (upper left side of heart) and the left main artery (lower right side of heart). (D) Calcification in the circumflex artery.

the patient denied exertional chest pain or anginal equivalents with his usual activities. His BP was mildly elevated despite therapy with a β blocker, diuretic, and an angiotensin-converting enzyme inhibitor. He had a residual right homonymous hemianopsia and mild memory impairment from his recent cerebrovascular accident. A resting echocardiogram estimated his ejection fraction at 49% with mild global left ventricular hypokinesis. His serum creatinine was 2.6 mg/dl. Despite cholesterol-lowering therapy, his total cholesterol was 168 mg/dl, the HDL cholesterol was 39 mg/dl, the LDL cholesterol was 80 mg/dl, and the triglycerides were 313 mg/dl. The total homocysteine was 17 μ M (range 0 to 13), and the high-sensitivity C-reactive protein was 0.673 mg/dl (normal <0.8). The cysteamine dosage regimen was 300 mg every 6 h, and his leukocyte cystine level was 2.6 nmol half-cystine/mg protein.

High resolution CT revealed evidence of several vascular calcifications, including bilateral calcification in the cavernous

portions of the internal carotid arteries (Figure 5). The chest and abdominal CT showed calcification in the right and left coronary arteries, within the aortic arch, and in the distal portion of the abdominal aorta.

Bicycle stress echocardiography revealed reversible myocardial ischemia. The test was stopped after only 5 min because of leg pain and shortness of breath. At peak exercise, 1-mm horizontal ST segment depression occurred in leads III and AVF, 1.5-mm horizontal depression occurred in leads II and V6, and 4-mm horizontal depression occurred in leads V4 and V5. The changes returned to baseline after 9 min of recovery. The echocardiogram demonstrated akinesis of the apex and hypokinesis of the mid-anterior and mid-lateral walls. The final impression was anterolateral ischemia and likely multivessel coronary artery disease. The decision was made first to institute more aggressive medical management for coronary artery disease and then to have the patient evaluated for bypass surgery by his medical team at home.

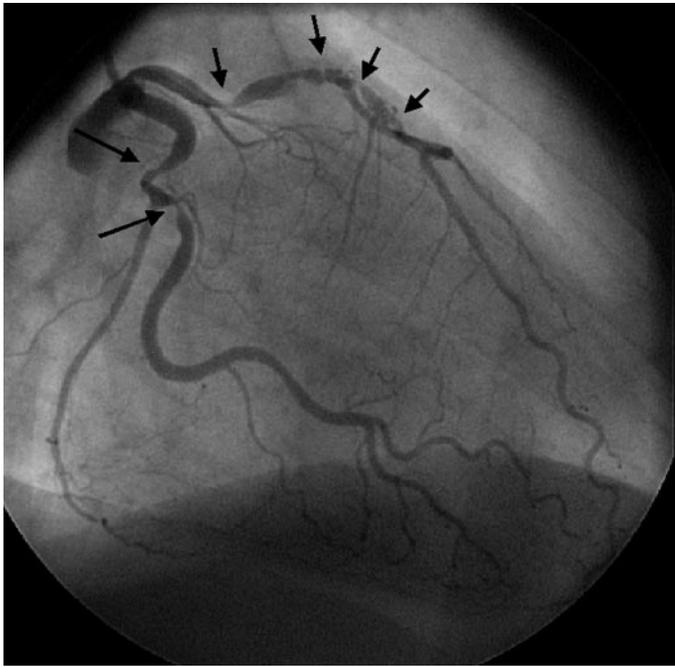


Figure 4. Coronary angiogram of patient 2. The large black arrows highlight high-grade occlusions in the proximal portion of the left circumflex and the obtuse marginal branch of the circumflex artery. The small black arrows highlight high-grade occlusions in the left anterior descending branch.

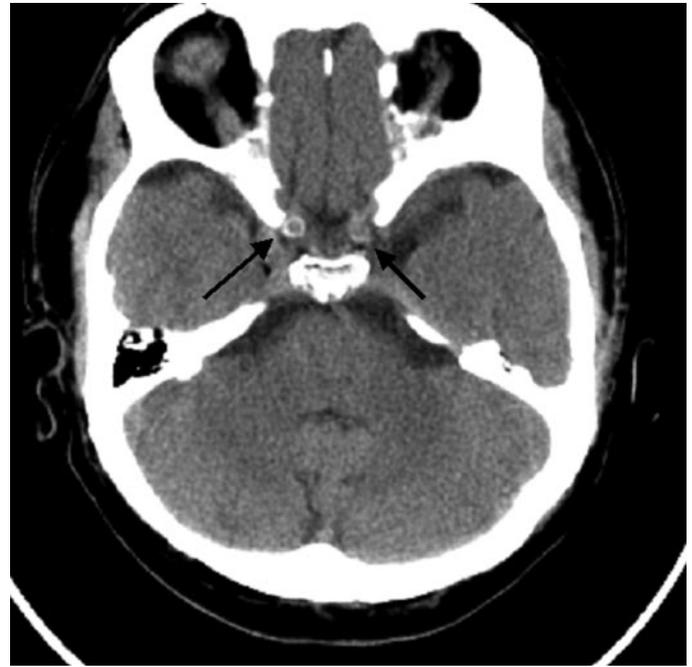


Figure 5. Calcifications on a coronal CT slice in the internal carotid arteries of patient 8. The black arrows point to calcification in the cavernous portion of the carotid arteries in this 37-yr-old man.

Discussion

The destruction of individual parenchymal cells, perhaps through enhanced activation of apoptotic mechanisms (29), is considered the basis for tissue injury in nephropathic cystinosis. This process affects the kidney very early; the thyroid gland in late childhood; and the pancreas, muscle, and central nervous system in early adulthood (1,2). Most likely, the full spectrum of extrarenal involvement in cystinosis has not yet been elucidated; many of the late complications of cystinosis were recognized only after renal transplantation allowed patients to survive past adolescence (27).

We now add arteriopathy to the list of late complications of poorly treated cystinosis. The frequency of this finding can only be estimated, but in our cohort, 13 of 41 individuals displayed calcification of various medium and large vessels, most notable the coronary arteries and the arteries that feed the circle of Willis. Our patients underwent routine CT scans of the head and chest and were not selected on the basis of signs of vascular or cardiac compromise.

The high prevalence of cardiovascular morbidity and mortality in patients with renal disease has been well documented (30–33), and our patients had several risk factors for vascular calcification and obstructive atherosclerosis. All 13 such patients in our cohort had endured renal failure and had undergone at least one renal allograft procedure. This frequency of renal transplantation (100%) was slightly greater than the frequency among patients who lacked calcifications (79%), but renal transplantation actually reduces the frequency of coronary artery calcification in patients with renal failure (34).

Nine of 13 patients with vascular calcifications had undergone previous dialysis. However, time on dialysis in this group did not differ significantly from that of the patients who had cystinosis and did not have vascular calcifications (Table 1).

Diabetes is another a major risk factor for atherosclerosis and coronary artery disease, and six (46%) of our 13 patients with vascular calcifications had diabetes (Table 1). This was significantly greater than the frequency of diabetes (2 of 28; 7%) in patients without calcifications and probably reflects the older age of the patients with calcifications; insulin dependence began at a mean age of 26 yr in our patients. Immunosuppressive agents such as tacrolimus and steroids also may have contributed to glucose intolerance among our posttransplantation patients (35–38).

Three of our 13 patients with vascular calcifications had total serum cholesterol levels >200 mg/dl, but this did not differ from the frequency for patients who did not have vascular calcifications (Table 1). Patients with posttransplantation cystinosis are known to exhibit elevations in total serum cholesterol (27).

Another possible risk factor for vascular calcifications in cystinosis involves abnormalities of calcium and phosphate homeostasis. Pretransplantation patients with cystinosis may develop medullary nephrocalcinosis (39), related to their urinary phosphate and calcium loads, which are substantially increased as a result of renal tubular Fanconi syndrome and the use of supplemental vitamin D to treat this complication. Ectopic calcification can occur in the basal ganglia and periventricular areas of the brain in posttransplantation patients who have cystinosis and have not received long-term cysteamine

therapy (16). However, serum calcium and phosphate levels in our patients with vascular calcification were not elevated. Moreover, the calcium-phosphate product, which strongly correlates with osteoblastic activity of vascular cells (40,41) and with the prevalence of vascular calcification (31–33), was not elevated in our patients. In fact, the average calcium-phosphate product was $38 \text{ mg}^2/\text{dl}^2$ (Table 1), similar to that of our patients without vascular calcifications ($41 \text{ mg}^2/\text{dl}^2$) and significantly lower than the average of $65 \text{ mg}^2/\text{dl}^2$ found in patients with coronary artery calcification and ESRD (32).

We could not attribute vascular calcification to hypertension, because our 13 posttransplantation patients with calcifications had the same frequency of hypertension (Table 1) as the 28 patients who lacked vascular calcifications. Other risk factors, such as hyperhomocysteinemia, increased C-reactive protein or advanced glycation end products, and markers of inflammation, could not be assessed because this was a retrospective analysis.

Outside of the moderately increased risk associated with diabetes, no specific risk factor or combination of risk factors for the development of vascular calcifications could be identified within our cohort of patients with cystinosis. Consequently, we propose that cystinosis itself is a risk factor for the development of vascular calcifications. Cystine continues to accumulate with age in cystinosis, and our affected patients were significantly older than their counterparts without vascular calcifications (Table 1). Moreover, the frequency of vascular calcifications was higher in patients who had been off cysteamine treatment for longer (Figure 1A) and was lower in patients who had been on cysteamine therapy longer (Figure 1B). Mechanistically, cysteamine lowers intracellular cystine stores, which may destroy individual vascular endothelial cells, resulting in secondary calcification. Cysteamine treatment has no known effect on the other putative risk factors for vascular calcifications.

Patients who have cystinosis and a history of chronic renal failure that necessitates dialysis and renal replacement therapy should be considered at high risk for the development of vascular calcifications and atherosclerosis. Beginning in early adulthood, these patients require careful monitoring and aggressive treatment to prevent the development of organ ischemia related to vascular calcification. Sustained oral cysteamine therapy should be provided to patients of all ages who have cystinosis to prevent the cellular destruction that results in tissue deterioration.

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