Nephropathic Cystinosis in Adults: Natural History and Effects of Oral Cysteamine Therapy

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Background: The full burden of nephropathic cystinosis in adulthood and the effects of long-term oral cysteamine therapy on its nonrenal complications have not been elucidated.

Objective: To assess the severity of cystinosis in adults receiving and not receiving oral cysteamine therapy.

Design: Case series.

Setting: National Institutes of Health Clinical Center.

Patients: 100 persons (58 men and 42 women) age 18 to 45 years with nephropathic cystinosis examined between January 1985 and May 2006.

Measurements: Historical data were collected on renal transplantation, administration of oral cysteamine, and time and cause of death. Patients were evaluated for height and weight; thyroid, pulmonary, and swallowing function; muscle atrophy; hypogonadism (in men); retinopathy; vascular and cerebral calcifications; diabetes mellitus; and homozygosity for the common 57-kb deletion in CTNS. Laboratory studies were also performed.

Results: Of 100 adults with nephropathic cystinosis, 92 had received a renal allograft and 33 had died. At least half of the patients had hypothyroidism, hypergonadotropic hypogonadism (in men), pulmonary insufficiency, swallowing abnormalities, or myopathy. One third of the patients had retinopathy or vascular calcifications, and 24% had diabetes. Homozygosity for the 57-kb CTNS deletion was associated with an increased risk for death and morbidity. The 39 patients who received long-term (>8 years) oral cysteamine therapy were taller and heavier, had a renal allograft later in life, had lower cholesterol levels, and experienced fewer complications and deaths than patients who received cysteamine for fewer than 8 years. The frequency of diabetes mellitus, myopathy, pulmonary dysfunction, hypothyroidism, and death increased as time off cysteamine treatment increased, and it decreased as time on cysteamine therapy increased.

Limitations: The study was retrospective and not randomized. The criteria used to measure adequacy of treatment were arbitrary.

Conclusions: Untreated nephropathic cystinosis causes extensive morbidity and death in adulthood. Long-term oral cysteamine therapy mitigates these effects.


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Nephropathic cystinosis, the most common identifiable cause of the renal Fanconi syndrome in childhood, is an autosomal recessive storage disease caused by defective transport of cystine out of lysosomes (1–3). The renal tubular damage of cystinosis, which begins at 6 to 12 months of age, is associated with polyuria, polydipsia, dehydrogenation, acidosis, hypophosphatemic rickets, hypokalemia, hypocalcemic tetany, hypocalcinemia, and growth retardation. These disorders are treated with nutritional replacements and, sometimes, growth hormone therapy. Renal glomerular damage generally becomes apparent by 2 to 5 years of age and results in end-stage renal disease by 9 to 10 years of age unless cystine-depleting therapy is initiated early in life (1–3). Renal replacement therapy has transformed cystinosis from an exclusively pediatric disease to one that affects individuals up to (and potentially beyond) 50 years of age.

Nonrenal complications of nephropathic cystinosis were initially thought to be limited to photophobia and hypothyroidism. Once kidney transplantation allowed survival past 10 years of age, the multisystemic nature of cystinosis became apparent (4). Complications include retinal blindness (5), vacuolar myopathy (6, 7), swallowing dysfunction (8, 9), diabetes mellitus (10), pancreatic exocrine insufficiency (11), central nervous system involvement (12, 13), pulmonary dysfunction (14), male hypogonadism (15), benign intracranial hypertension (16), vascular calcifications (17), and nodular regenerating hyperplasia of the liver (18).

The basic defect in cystinosis was elucidated in 1982 (1, 2), and the causative gene, CTNS (OMIM 606272), was discovered in 1998 (19). CTNS is located on chromosome 17p (20) and encodes cystinosin, a 367–amino acid protein with 7 transmembrane domains (19). Cystinosin transports the disulfide amino acid cystine out of lysosomes and into the cytoplasm of cells, where it is reduced to cysteine. This transport process is defective in cystinosis (21–23), causing intralysosomal accumulation and, in most cells, crystal formation (Figure 1). This pathologic process is attenuated in some variants of cystinosis with residual transport activity (24). Specifically, onset of renal disease in adolescence indicates intermediate cystinosis (2, 25), and photophobia due to corneal crystals is the only symptom of ocular cystinosis (also called nonnephropathic cystinosis) (2, 26).

Targeted therapy for nephropathic cystinosis involves...
oral administration of the free aminothiol cysteamine (27). This membrane-permeable compound enters lysosomes, where it participates with cystine in a disulfide interchange reaction, forming cysteine and cysteine–cysteine mixed disulfide (28), both of which can exit the cystinotic lysosome by using transporters other than the defective cystinosin (29). Oral cysteamine (Cystagon, Mylan Pharmaceuticals, Morgantown, West Virginia), which was approved by the U.S. Food and Drug Administration in 1994, is given every 6 hours at a dosage of 60 to 90 mg/kg of body weight per day (1.3 to 1.95 g/m² of height per day). When adherence is consistent, this therapy achieves leukocyte cystine depletion of up to 95% and reduces the cystine content of parenchymal tissues, such as the muscle and liver (30). Oral cysteamine therapy preserves renal glomerular function, enhances growth, and obviates the need for L-thyroxine replacement therapy (31–33). It also prevents the development of swallowing difficulties (9), coronary artery calcifications (17), and damage to the posterior segment of the eye (34). In addition, topical cysteamine eye drops dissolve the corneal crystals of cystinosis (35–37).

We present the clinical characteristics of 100 adults with nephropathic cystinosis who were examined at the National Institutes of Health (NIH) Clinical Center between 1985 and 2006. Untreated cystinosis is a devastating disease, with a 33% mortality rate and nearly universal morbidity in adults. Long-term oral cysteamine administration has substantial beneficial effects on survival and final height and weight and helps prevent diabetes mellitus, myopathy, pulmonary dysfunction, and hypercholesterolemia, which are associated with nephropathic cystinosis.

**METHODS**

Patients

All patients were enrolled in NIH Clinical Center protocol 78-HG-0093, “Use of Cysteamine in the Treatment of Cystinosis,” and gave written informed consent to participate. The protocol was approved by the National Human Genome Research Institute Institutional Review Board and is consistent with the principles of the Declaration of Helsinki. Patients seen only for ophthalmic evaluation and those with intermediate or ocular cystinosis were excluded. Otherwise, every patient with classic nephropathic cystinosis who was admitted to the NIH Clinical Center between January 1985 and May 2006 and was at least 18 years of age at admission was included. Data from each patient’s latest admission were examined. This process resulted in analysis of data from 100 consecutive patients, of whom 35 were described in 1993 (38). Twenty-four of the 35 patients have since had follow-up admissions.

The diagnosis of nephropathic cystinosis was based on a typical history, the presence of corneal crystals, and an off-treatment polymorphonuclear leukocyte cysteine level greater than 3 nmol half-cystine/mg protein (normal value, <0.2 nmol half-cystine/mg protein; range in cystinosis, 3 to 25 nmol half-cystine/mg protein) (1–3). Cystine depletion was considered adequate if the leukocyte cystine level was less than 2.5 nmol half-cystine/mg protein 5 to 6 hours after a dose of oral cysteamine. Cystine was measured by using the cystine binding protein assay (39). Adherence to therapy was assessed independent of evaluation of complications of cystinosis.

Criteria for Diagnosis of Complications

Hypothyroidism was always treated in our patients with cystinosis and was diagnosed if a patient was receiving L-thyroxine replacement therapy. Hypogonadism was diagnosed if a male patient was receiving testosterone replacement, had a low serum testosterone level, or had a follicle-stimulating hormone concentration greater than 30 U/L (normal range, 1 to 12 U/L). Sexual development was evaluated by using the stages of Marshall and Tanner (40, 41), ranging from prepubertal (stage I) to fully developed (stage V). Patients were considered to have pulmonary dysfunction if their mean FVC, FEV₁, total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLco) values were less than 80% of predicted values. Swallowing abnormalities were diagnosed on the basis of a detailed examination showing at least mild impairment according to the published Swallowing Severity Score and Oral Muscle Composite Score (9). Myopathy was defined clinically by wasting of the distal muscles of the hand. Hypercholesterolemia was defined as a total serum cholesterol greater than 5.2 mmol/L (>200 mg/dL) or current receipt of a statin drug to treat hypercholesterolemia. Retinopathy was de-
fined by clinical examination, legal blindness in at least 1
eye, or an abnormal electroretinogram. Vascular and cere-
bral calcifications were identified by computed tomogra-
phy of the chest and brain, respectively. Diabetes mellitus
was diagnosed if patients required insulin therapy.

**Molecular Diagnostic Techniques**

Mutation analysis of the *CTNS* gene was done by us-
ing a multiplex method to detect the 57-kb deletion, which
is present in approximately 50% of North American pa-
tients (42–44).

**Role of the Funding Source**

The study received no external funding.

**RESULTS**

**General Characteristics**

One hundred patients age 18 to 45 years (mean age,
26.2 years [SD, 6.5]) who had cystinosis met our criteria
for analysis. The male-to-female ratio was 58:42. Of the 44
patients who were evaluated for sexual development, 1 was
Tanner stage I, 2 were stage II, 6 were stage III, 21 were
stage IV, and 14 were stage V. Three women each delivered 1
healthy child. The leukocyte cystine level while not receiv-
ing cysteamine therapy was available for 32 patients; the mean
value was 8.3 nmol half-cystine/mg protein (SD, 3.6).

**Kidney Transplantation**

Most patients (92%) had received a renal allograft
(Table 1), and many received more than 1. For all 92
patients who received a transplant, the first allograft was done at a mean age of 12.3 years (SD, 4.2). Of the 92 initial allografts, 42 were from living donors and 42 were from cadavers; for 8 allografts, the donor was not specified. Forty-four patients received a second renal transplant (13 from living donors, 29 from cadavers, and 2 from an unspecified source), and 6 patients received a third renal transplant (3 from living donors and 3 from cadavers). Seven of the 8 patients with native kidneys were 18 to 21 years of age, and 1 was 27 years of age.

Of the 92 patients who underwent transplantation, 17 were uremic at the time of their most recent NIH admission. Laboratory data, which were available for 74 of the remaining 75 patients, showed a slightly low mean hemoglobin level (12.0 g/L [normal range, 12.7 to 16.7 g/L]) but normal mean leukocyte count (6.8 × 10^9 cells/L) and platelet count (222 × 10^9 cells/L). The mean serum alanine aminotransferase level was 21 U/L (normal range, 6 to 41 U/L). The mean serum creatinine concentration was 125 μmol/L (1.4 mg/dL) (normal range, 80 to 124 μmol/L [0.9 to 1.4 mg/dL]), and mean 24-hour urinary protein excretion was elevated (295 mg [normal range, 30 to 150 mg]).

Nonrenal Complications

A large proportion of patients had hypothyroidism due to thyroid gland dysfunction (75%), hypergonadotropic hypogonadism (74% of men), pulmonary insufficiency (69%), swallowing abnormalities (60%), myopathy (50%), hypercholesterolemia (33%), retinopathy (32%), vascular calcifications (31%), diabetes mellitus (24%), or cerebral calcifications (22%). Figure 1 shows a typical patient with short stature and muscle wasting and corneal cystine crystals on electron microscopy.

Deaths

Thirty-three of the 100 patients died at a mean age of 28.5 years (SD, 6.1) (range 18 to 43 years). Their mean age at last admission was 26.0 years, which was almost the same as the age at last admission for the 67 adults who survived (26.2 years). Patients who died had received oral cysteamine for a mean (±SE) of 2.1 ± 0.7 years, compared with 9.6 ± 0.9 years for the 67 surviving patients. All patients who died had received a renal allograft at a mean age of 11.3 years (SD, 3.7).

Most patients had multisystemic involvement at the time of death. Nine patients died of sepsis, of whom 3 had bowel perforations and 3 had peritonitis. Five died of uremia; 2 of these patients had declined continuation of dialysis. Five patients died of respiratory complications (mean FVC, 39.0% of predicted [SD, 12.1%]; mean TLC, 49.6% [SD, 14.6%]; mean DLCO, 35.4% [SD, 16.4%]). All 5 had swallowing abnormalities and markedly reduced pulmonary function, and 4 had muscle wasting. Four of these 5 patients died of pneumonia (2 with documented aspiration), and 1 died of atelectasis, having declined ventilator support. Three patients died of portal hypertension; nodular regenerating hyperplasia was documented in 2 of these patients (18). One central nervous system death was attributed to a cerebrovascular accident, and the other was due to dystonic quadriplegia and pseudobulbar palsy (38, 45). Of 8 patients with an unknown cause of death, 7 had severe muscle wasting and swallowing abnormalities.

Effects of Cysteamine Therapy

To evaluate the influence of oral cysteamine therapy, we determined the frequency of a complication for each 10-year span that a patient either lived without adequate cysteamine treatment or continued cysteamine treatment diligently (0 to 10 years, 11 to 20 years, and so forth). Adherence to oral cysteamine therapy was determined by history for the years that a patient was not followed at the NIH and by leukocyte cystine values for the years that a patient was seen at the NIH.

The frequency of diabetes mellitus increased dramatically from 4% to 50% as the time off oral cysteamine therapy increased from less than 10 years to more than 30 years (Figure 2). In contrast, the frequency of diabetes decreased from 28% to 0% as the time on therapy increased to greater than 20 years (Figure 2). Similarly, the frequency of myopathy increased from 12% to 80% as time off cysteamine increased and decreased from 60% to 0% as time on therapy increased to greater than 20 years (Figure 2). No patient has received cysteamine for more than 30 years.

Pulmonary dysfunction increased in frequency and severity with time off cysteamine therapy and decreased with time on cysteamine therapy (Figure 2). For the 21 patients who lived without cysteamine therapy for 10 years or fewer, the mean FVC was 86% (SD, 20%) of predicted, compared with 56% (SD, 17%) for the 10 patients who lived without cysteamine therapy for more than 30 years. For the 53 patients who received cysteamine therapy for 10 years or fewer, the mean FVC was 54% (SD, 19%) of predicted, compared with 83% (SD, 22%) for the 24 patients who received cysteamine therapy for more than 10 years.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, n/n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received a transplant</td>
<td>92/100 (92)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>75/100 (75)</td>
</tr>
<tr>
<td>Hypogonadism (in men)</td>
<td>39/53 (74)</td>
</tr>
<tr>
<td>Pulmonary dysfunction†</td>
<td>53/77 (69)</td>
</tr>
<tr>
<td>Swallowing abnormality</td>
<td>58/97 (60)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>50/100 (50)</td>
</tr>
<tr>
<td>Hypercholesterolemia‡</td>
<td>31/94 (33)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>32/100 (32)</td>
</tr>
<tr>
<td>Vascular calcifications</td>
<td>16/52 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus requiring insulin therapy</td>
<td>24/100 (24)</td>
</tr>
<tr>
<td>Cerebral calcifications</td>
<td>21/95 (22)</td>
</tr>
<tr>
<td>Deceased</td>
<td>33/100 (33)</td>
</tr>
</tbody>
</table>

* Not all patients were evaluated for every characteristic.
† Mean values for FVC, FEV1, total lung capacity, and diffusing capacity for carbon monoxide were less than 80% of predicted values.
‡ Total serum cholesterol level >5.2 mmol/L (>200 mg/dL).
One hundred adults with cystinosis received cysteamine for a certain period of time and then did not receive cysteamine for a defined period of time, and each patient had or did not have a specific complication at the time of admission. Duration of cysteamine therapy was grouped in 10-year increments. The frequencies of diabetes, myopathy, pulmonary dysfunction, and death increased with time off cysteamine therapy and decreased with time on cysteamine therapy.
patients who received adequate treatment, data were available for a mean of 7.6 of the 8 complications; these patients had a mean of 2.2 insults (SD, 2.2). When 5 years of cysteamine treatment was chosen as the criterion for substantial therapy, 49 adequately treated patients had a mean of 2.4 complications (SD, 2.4) and 51 inadequately treated patients had a mean of 3.8 insults (SD, 2.0).

### Homozygosity for the 57-kb Deletion in CTNS

Of 79 patients who had mutation analysis, 34 were homozygous for the 57-kb CTNS deletion (44) and 45 were not homozygous but had at least 1 other CTNS mutation. These 2 groups had similar mean ages (28.0 years [SD, 6.9] vs. 26.3 years [SD, 6.4], respectively) and mean durations of cysteamine administration (7.4 years [SD, 7.1] vs. 9.2 years [SD, 7.7]). Nevertheless, more deaths (12 of 34 [35%] vs. 6 of 45 [13%]; chi-square, 5.3) and complications (mean, 4.3 of a possible 7.3 [SD, 2.0] vs. 2.7 of a possible 7.5 [SD, 2.4]) occurred among patients who were homozygous for the deletion than among patients who were not homozygous.

In theory, the beneficial effects of cysteamine therapy could be attributed in part to a genetic predisposition to more severe disease, if patients who are homozygous for the 57-kb CTNS deletion were overrepresented among patients who received inadequate cysteamine therapy. However, no such skewing occurred. With respect to duration of cysteamine treatment (Figure 2), 25% to 42% of patients in the 7 time cells (0 to 10, 11 to 20, 21 to 30, and 31 to 40 years off treatment and 0 to 10, 11 to 20, and 21 to 30 years on treatment) were homozygous for the deletion. With respect to the dichotomous analysis involving substantial cysteamine therapy (Table 2), 33% of the 61

| Table 2. Clinical Characteristics of Patients Who Received Long-Term Oral Cysteamine Therapy* |
|-----------------------------------|-----------------------------------|
| **Characteristic**                | **Duration of Cysteamine Therapy** |
|                                  | <8 Years | ≥8 Years |
|                                  | (n = 61) | (n = 39) |
| Age, y                           | 26.4 (6.0) | 25.8 (7.3) |
| Time on cysteamine therapy, y    | 2.0 (2.4) | 15.1 (5.4) |
| Time off cysteamine therapy, y   | 24.3 (5.9) | 10.7 (10.1) |
| Height, cm                       | 143.6 (11.2)† | 154.7 (10.8) |
| Weight, kg                       | 45.3 (10.7) | 53.2 (10.4) |
| Age at transplantation, y        | 11.0 (3.2) | 14.8 (4.6)† |
| Serum cholesterol level§         | 5.05 (1.48) | 4.40 (1.06) |
| mg/dL                            | 199 (57) | 170 (41) |
| Complications per patient, n/n (%) | 4.0 (2.0) | 2.2 (2.2) |
| Hypothyroidism, n/n (%)           | 53/61 (87) | 22/39 (56) |

* Values are presented as means (SD) unless otherwise indicated.† Based on 60 patients. § Based on 51 patients. ¶ Normal range, 2.6 to 5.2 mmol/L (100 to 200 mg/dL). II Eight possible complications were included: hypothyroidism, pulmonary dysfunction, swallowing abnormalities, myopathy, retinopathy, vascular calcifications, diabetes mellitus, and cerebral calcifications. On average, data were available for 7.0 of the 8 complications among persons who received cysteamine <8 years and 7.6 of the 8 complications among those who received cysteamine ≥8 years.

years. The frequency of death also increased with time off cysteamine therapy and decreased with time on cysteamine therapy (Figure 2).

Among the 48 adults with cystinosis who went without oral cysteamine therapy for at least 20 years, the frequencies of diabetes, myopathy, death, and pulmonary dysfunction were 38%, 73%, 48%, and 87%, respectively. Among the 5 patients who received oral cysteamine therapy for more than 20 years, the frequencies of diabetes, myopathy, and death were all 0%; 1 patient had mild pulmonary dysfunction (FVC, 60% of predicted; TLC, 67% of predicted; DLCO, 65% of predicted). Nine patients did not experience the nonrenal complications described in Table 1; all were 18 to 21 years of age and had received oral cysteamine therapy for 13 to 19 years (mean duration, 16.0 years [SD, 2.0]). Three of the 9 patients had had transplantation.

We compared patients who received substantial oral cysteamine therapy with patients who did not receive such therapy. We arbitrarily defined “substantial” as 8 years because this criterion allowed us to analyze a large number of patients (39 of 100) as adequately treated and because it effectively differentiated inadequately treated patients from adequately treated patients in terms of duration of therapy. In fact, the 61 inadequately treated patients received cysteamine for only 2.0 years on average, compared with 15.1 years in the 39 adequately treated patients (Table 2). The mean height (144 cm) and weight (45 kg) of inadequately treated patients were nearly identical to those reported elsewhere for adults with cystinosis (144 cm and 44 kg, respectively [38]). Adequately treated patients had statistically significantly greater height and weight, but their mean height (155 cm) was still 4 cm below the normal third percentile, and their mean weight was only 3 kg above the normal third percentile. Of the 100 patients whom we studied, all 8 with functioning native kidneys had received cysteamine for at least 8 years; the 31 adequately treated patients who had had transplantation received their allografts, on average, 3.8 years later than the 61 inadequately treated patients (Table 2). Hypothyroidism occurred less frequently in adequately treated patients than in poorly treated patients (56% vs. 87%; chi-square, 11.8). Only 8% of adequately treated patients had died, compared with 49% of inadequately treated patients (chi-square, 18.5). Adequately treated patients had cholesterol levels that were on average 0.65 mmol/L (25 mg/dL) lower than those in inadequately treated patients (Table 2).
adequately treated patients and 36% of the 39 inadequately treated patients were homozygous for the 57-kb deletion.

**DISCUSSION**

Before 1960, every person born with cystinosis died in infancy because of the renal Fanconi syndrome or in the first decade of life because of chronic glomerular failure. In the late 1960s, renal allograft procedures for children dramatically increased the longevity of these patients, but the effects of kidney losses remain unremitting: Seventeen of our 92 patients who had transplantation were uremic. Moreover, long-term cystine accumulation continued to damage nonrenal tissues. Organs previously thought to be spared by cystinosis, such as the brain, the liver, and muscle, became affected (2). Initial reports described only a few cases of each late complication. Now, as children with cystinosis survive into adulthood, the true burden of disease conferred by mutations in CTNS, especially homozygosity for the 57-kb deletion, has become clear. Specifically, the mortality rate of cystinosis in adulthood approximates one third, and death generally occurs before 30 years of age. The causes of death among patients with cystinosis are varied and somewhat expected, but a new finding is involvement of the gastrointestinal tract: Three bowel perforations and 3 fatal incidents of peritonitis implicate chronic intestinal damage as a cause of death.

Morbidity in cystinosis takes many forms. Thyroid gland fibrosis results in hypothyroidism, with a frequency of 75% in our study. This frequency, which is lower than that reported elsewhere at age 30 years (90% [33]), probably reflects improved treatment with cysteamine. Male hypergonadotropic hypogonadism, which is due to testicular fibrosis and atrophy (15), is treated with testosterone replacement therapy. None of our male patients has fathered a child.

Myopathy, swallowing difficulty, and pulmonary dysfunction are grouped together because they all relate to muscle disease. Muscle cystine content increases with age among patients with cystinosis who are not receiving cysteamine therapy (30); weakness and atrophy progress distal to proximal. Pharyngeal muscle involvement leads to swallowing dysfunction and thoracic muscle weakness impairs pulmonary function; these are proximate causes of death in adults with cystinosis. The 50% frequency of myopathy in our study slightly exceeds the 33% reported elsewhere (38), and the 60% frequency of swallowing abnormalities exactly matches that found in 1993 (38).

Mild hypercholesterolemia, which was observed in our patients, is well recognized in cystinosis (4). The fact that cysteamine therapy was associated with lower cholesterol levels suggests that hypercholesterolemia is related to cystinosis, although some influence of glomerular dysfunction, proteinuria, and glucocorticoid treatment cannot be excluded. If diet and exercise do not reduce serum cholesterol levels to normal values, use of a cholesterol-lowering statin should be considered, particularly in view of the known vascular complications of cystinosis (17).

Diabetes mellitus in cystinosis reflects damage to the pancreas that may also affect its exocrine function (10, 11). One quarter of our adult patients required insulin, compared with 5 of 36 (14%) patients in a previous study (38). In some cases, hyperglycemia may be exacerbated by prednisone therapy used to prevent renal allograft rejection. However, the prophylactic effect of long-term oral cysteamine treatment supports the claim that cystine accumulation plays a role.

The prognostic significance of basal ganglia and periventricular calcifications, often accompanied by cerebr al atrophy (13), remains uncertain. We surmise that the calcifications reflect previous parenchymal damage.

Our study has limitations. We performed a retrospective analysis of patients receiving different oral cysteamine regimens. Patients could not be randomly assigned to cysteamine therapy or no therapy because adherence could not be ensured and because the known beneficial effects of cysteamine therapy made it ethically questionable to withhold the drug from patients desiring it. In any event, the salutary effect of oral cysteamine provides a modicum of hope to counter the dire outcomes and grave prognoses associated with cystinosis after renal transplantation. In fact, the frequency of complications listed in Table 1 may be lower than that dictated by the natural history alone, because many of the patients were receiving cystine-depleting therapy. Although the effects of cystine accumulation do not seem to be reversible, they can be prevented by long-term cysteamine administration, which has been shown to be associated with lower frequencies of hypothyroidism (33), swallowing abnormalities (9), vascular calcifications (17), and posterior eye segment defects (34) in patients of all ages with cystinosis. We found that the frequencies of several complications of cystinosis increased with time off cysteamine therapy and decreased with greater time on cysteamine treatment (Figure 2). This was true for type 1 diabetes mellitus, myopathy, pulmonary dysfunction, hypothyroidism, and death. Cysteamine therapy also had a beneficial effect on adult height, adult weight, and serum cholesterol levels (Table 2).

Oral cysteamine therapy is taken every 6 hours to achieve continuous cystine depletion, as gauged by leukocyte cystine levels. Our criterion for adequate cysteamine therapy included maintenance of leukocyte cystine values less than 2.5 nmol half-cystine/mg protein. We believe that greater cystine depletion is preferable but difficult to achieve because cysteamine tastes and smells foul. Efforts are under way to develop a cysteamine preparation with release in the small intestine, which might allow administration every 12 hours (46).

Oral cysteamine therapy has such proven efficacy in preventing renal glomerular damage that the U.S. Food and Drug Administration has approved it for use in pre-
transplantation cystinosis. When patients progress to renal failure despite cysteamine therapy, often at age 20 years rather than age 10 years, renal transplantation rescues them from dialysis or uremia. However, organ replacement is not available for other systems damaged by cystine. Consequently, the only therapeutic option is oral cysteamine, which substantial evidence indicates is safe and effective in preventing late complications. This finding has 2 major implications. First, cysteamine therapy should be considered for all patients with cystinosis, regardless of age and transplantation status (47). In addition, the registration for cysteamine bitartrate should be reevaluated to include among its indications posttransplantation cystinosis and its associated nonrenal organ damage.

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