Pulmonary Dysfunction in Adults With Nephropathic Cystinosis*

Yair Anikster, MD; Felicitas Lacbawan, MD; Mark Brantly, MD; Bernadette L. Gochuico, MD; Nilo A. Avila, MD; William Travis, MD, FCCP; and William A. Gahl, MD, PhD

Objective: To characterize the pulmonary dysfunction in patients with nephropathic cystinosis after renal transplantation.

Design: Cross-sectional analysis of consecutive adult patients.

Patients: Twelve adult, nephropathic cystinosis patients and 3 adult, ocular, nonnephropathic cystinosis patients admitted to the National Institutes of Health Clinical Center.

Results: The 12 nephropathic cystinosis patients (age range, 21 to 40 years) showed an extraparenchymal pattern of restrictive lung disease, with inspiratory and expiratory dysfunction. Specifically, the mean FVC was 58% of predicted, the mean FEV₁ was 57% of predicted, and the mean total lung capacity was 66% of predicted, while the mean residual volume was normal. Furthermore, the mean maximal inspiratory pressure for the eight patients tested was 40% of predicted, and the mean maximal expiratory pressure was 26% of predicted. Two patients died of respiratory insufficiency. All the patients had lived at least 17 years, while lacking compliant cystine-depleting therapy with oral cysteamine. Seven patients had a conical chest, restricting excursion, and 10 of the 12 patients had evidence of the myopathy that typifies late cystinosis. In fact, the severity of pulmonary disease correlated directly with the severity of myopathy in our group of 12 patients. In contrast, the lung parenchyma was essentially normal, as gauged by chest radiographs and CT scans of the lung. The three patients with nonnephropathic cystinosis displayed entirely normal pulmonary function.

Conclusion: The distal myopathy characteristic of nephropathic cystinosis results in an extraparenchymal pattern of restrictive lung disease in adults who have not received long-term cystine depletion. Whether or not oral cysteamine therapy can prevent this complication remains to be determined.

(CHEST 2001; 119:394–401)

Key words: CT scan; myopathy; pulmonary function tests; restrictive lung disease

Abbreviations: EMG = electromyogram; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; MVV = maximal voluntary ventilation; RV = residual volume; TLC = total lung capacity

Cystinosis, an autosomal recessive lysosomal storage disease, occurs due to deficiency of a cystine carrier in the lysosomal membrane. In the absence of its transporter, free, nonprotein cystine accumulates within lysosomes and crystallizes in many tissues, including the kidney, liver, intestine, spleen, and cornea. The most common type of cystinosis, involving approximately 95% of cystinosis patients, is called nephropathic or infantile cystinosis. This disorder is characterized by renal tubular Fanconi syndrome at 6 to 12 months of age, along with failure to thrive, polyuria, dehydration, hypophosphatemic rickets, photophobia, and hypothyroidism. Glomerular damage results in renal failure at approximately 10 years of age, and this must be treated with dialysis or a renal allograft procedure. The natural history of nephropathic cystinosis can be favorably altered by long-term administration of the free thiol cysteamine, or mercaptoethylamine, which lowers the cystine content of leukocytes and a variety of other cell types. Oral cysteamine therapy has proven efficacy in preventing renal deterioration, improving growth, and obviating the need for L-thyroxine replacement in nephropathic...
cystinosis. In addition, cysteamine eye drops dissolve the corneal cystine crystals of cystinosis patients.10,11

Adolescent or intermediate cystinosis resembles nephropathic cystinosis, but with later onset of renal disease.1 Ocular or nonnephropathic (formerly “benign” or “adult”) cystinosis is associated with photophobia due to corneal crystal formation, but no renal disease.12 The three types of cystinosis are allelic in nature,13–16 all due to mutations in the CTNS gene.17 The most common mutation in CTNS is a 57-kb deletion17–20 causing nephropathic cystinosis. Individuals heterozygous for cystinosis are always entirely normal.

The continued accumulation of intracellular cystine after renal transplantation causes a variety of complications in patients not treated with cysteamine.21 They include a distal vacuolar myopathy,22,23 swallowing difficulty,24,25 retinal blindness,26 pancreatic endocrine26 and exocrine27 insufficiency, male hypogonadism,28 and neurologic deterioration.29,30 Although nearly every tissue and organ system appears to be involved eventually, lung disease has not been reported in this disorder. Having encountered pulmonary dysfunction in our adult cystinosis patients, we decided to characterize the extent and possible cause of this late complication of nephropathic cystinosis. Evidence indicates that the lung dysfunction of cystinosis is related to extrinsic muscle impairment rather than primary parenchymal disease.

**Materials and Methods**

**Patients**

We investigated cystinosis patients who were admitted to the National Institutes of Health Clinical Center between July 1997 and June 1998, and who had lived at least 17 years without cysteamine therapy. Twelve adult patients with nephropathic cystinosis and 3 patients with ocular, nonnephropathic cystinosis fit these criteria. The nephropathic cystinosis patients had each previously received a renal allograft. All the patients were enrolled in protocols approved by the National Institute of Child Health and Human Development Institutional Review Board. The subjects underwent a thorough pulmonary evaluation that included a clinical assessment, pulmonary function tests, chest radiograph, high-resolution thin-section CT scan of the chest, and genotype analysis.

**Genetic Studies**

Molecular analyses for the 57-kb deletion19 and for other individual mutations15,18 were performed as described. Patients 5 and 9 in the current article are identical to patients 24 and 9 in the article by Shotelersuk et al.18 The ocular cystinosis patients (patients 13, 14, and 15) correspond to patients 3, 4, and 1, respectively, of the study by Aukster et al.15

**Pulmonary Function Tests**

Pulmonary function tests were performed as described.31 Maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and maximum voluntary ventilation (MVV) were obtained using pulmonary function modules (Collins Medical; Braintree, MA, and Erich Jaeger; Millbury, OH). To test MIP, patients inhaled completely, and then exhaled with lips sealed around a mouthpiece and with as much force as possible. To test MEP, patients inhaled completely, and then exhaled with as much force as possible. For MVV testing, patients were prompted to exert maximal effort by performing deep breathing as rapidly as possible for 12 to 15 s. Test results were selected and reported in accordance with published guidelines from the American Thoracic Society.32,33

**Evaluation of Myopathy**

Seven of 12 nephropathic cystinosis patients underwent electromyography, and all patients had a swallowing evaluation. The severity of the myopathy was gauged using a three-tiered scoring system in which “0” indicates at most very mild muscle weakness or swallowing difficulty, “+” corresponds to moderate muscle weakness or atrophy on physical examination or an electromyogram (EMG) diagnostic of myopathy, plus some swallowing difficulty, and “++” indicates severe wasting and weakness involving the arms and shoulders, with moderate to severe impairment of swallowing.

**Results**

Twelve nephropathic cystinosis patients (age range, 21 to 40 years) exhibited decreased values for mean FVC, FEV1, and total lung capacity (TLC; Table 1). Values for mean MVV, MIP, and MEP obtained from eight patients were even further depressed, whether expressed as percentage of predicted (Table 1) or as absolute values compared with normal values (Table 2).34 Mean residual volume (RV) and diffusing capacity of the lung for carbon monoxide adjusted for lung volumes were normal, and mean RV/TLC was increased. In this limited group of posttransplant patients, there was no correlation between impaired pulmonary function and age, gender, or immunosuppressive medications. In addition, patients homozygous for the common 57-kb deletion in CTNS had pulmonary function values no different from those of patients bearing one of the other mutations. There were insufficient data to determine if long-term cysteamine therapy correlated with better pulmonary function. However, each of the 12 patients studied had lived at least 17 years without compliant cysteamine therapy. Three ocular cystinosis patients with normal stature and renal function displayed normal pulmonary function test results as well (Table 1).

For all 12 patients, the respiratory rate remained between 16 breaths/min and 22 breaths/min, and the oxygen saturation was between 95% and 100% on room air. Other symptoms and signs of respiratory
compromise varied considerably. Patients 2, 3, 4, 5, 7, 8, 9, 10, and 11 had no respiratory complaints, patient 6 complained of dyspnea at night, and patients 1 and 12 died of respiratory insufficiency.

Chest radiography, performed on 11 patients, showed normal lung parenchyma in 9 patients but slightly increased interstitial markings in patient 7 and left base atelectasis in patient 12. In addition, seven patients exhibited a conical chest cavity (Fig 1) and five patients had mild gastric dilatation. High-resolution, thin-section CT scans of the chest were also performed on 11 patients. The lung parenchyma was normal in nine patients, while patient 7 exhibited a punctate density in the pleura of the right upper lobe and patient 12 showed minimal scarring of the left lower lobe. Echocardiography, performed on 10 patients, showed no evidence of pulmonary hypertension or cardiac dysfunction.

The absence of primary pulmonary parenchymal disease prompted investigation into other causes of impaired pulmonary function. There was no correlation of pulmonary disease with renal failure, as indicated by the normal serum creatinine values in 10 of 12 patients (Table 3). However, several of the 12 patients having impaired pulmonary function also suffered from muscle disease. In fact, a myopathy typical for cystinosis was clinically prominent in patients 1 (Fig 2, top), 6, 8, and 12 (Fig 2, bottom), and was present to a lesser degree in patients 2, 4, 7, and 10 (Table 3).

Electrophysiologic findings supported the clinical impression of a myopathic process. In patient 1, the EMG showed a muscle disorder affecting distal and proximal upper-extremity muscles with evidence for membrane irritability in the proximal arm muscles. There was EMG evidence for involvement of the lower facial muscles as well. The respiratory system was affected, with membrane irritability noted in both the intercostal muscles and the diaphragm, and it was observed that the intercostal muscles were being used even during quiet breathing. In patient 6, an EMG and nerve conduction study showed a significant myopathy with muscle membrane irritability, prominent distally. For patient 8, a needle EMG revealed evidence for primary muscle disease with muscle membrane irritability. The respiratory muscle did not appear to be involved in the myopathic process, although recruitment of the intercostal muscles during quiet respiration was noted. A biopsy specimen of the left abductor digiti minimi in 1993 revealed marked fiber-size variation, internal nuclei, and rimmed vacuoles, with no endomesial inflammation; the findings were characteristic of a vacuolar myopathy. The EMG of patient 9 showed evidence for a primary disease of the muscles, with muscle membrane irritability. A previous study in 1990 had revealed myopathic findings in an intrinsic hand muscle but not in the biceps. The presence of myopathic abnormalities in the biceps brachii on the more recent examination was considered to indicate

Table 1—Pulmonary Function Characteristics of Cystinosis Patients*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr/Sex</th>
<th>CTNS Mutation</th>
<th>Age at Tx, yr</th>
<th>Transplant Medications</th>
<th>Duration of MEA, yr</th>
<th>Pulmonary Function (% Predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FVC FEV&lt;sub&gt;1&lt;/sub&gt; TLC RV TLC D/VA MVV MIP MEP</td>
</tr>
<tr>
<td>Nephropathic cystinosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21/F</td>
<td>57-kb del/57-kb del</td>
<td>6</td>
<td>P, A</td>
<td>3</td>
<td>23 27 72 229 318 96 19 19 8</td>
</tr>
<tr>
<td>2</td>
<td>22/F</td>
<td>W137X/W137X</td>
<td>4</td>
<td>P, A, C</td>
<td>5</td>
<td>48 52 58 95 164 53 34 51 24</td>
</tr>
<tr>
<td>3</td>
<td>24/F</td>
<td>ND/ND</td>
<td>15</td>
<td>P, A, C</td>
<td>5</td>
<td>75 69 68 41 61 119 63 50 22</td>
</tr>
<tr>
<td>4</td>
<td>24/M</td>
<td>57-kb del/57-kb del</td>
<td>11</td>
<td>P, A</td>
<td>3</td>
<td>55 51 62 96 156 83 — — —</td>
</tr>
<tr>
<td>5</td>
<td>25/M</td>
<td>G339R/G339R</td>
<td>11</td>
<td>P, C</td>
<td>2</td>
<td>73 67 82 132 161 70 — — —</td>
</tr>
<tr>
<td>6</td>
<td>26/M</td>
<td>ND/ND</td>
<td>10</td>
<td>A</td>
<td>0</td>
<td>36 37 37 40 110 88 38 30 33</td>
</tr>
<tr>
<td>7</td>
<td>26/M</td>
<td>57-kb del/57-kb del</td>
<td>10</td>
<td>P, A, C</td>
<td>0</td>
<td>55 52 66 113 171 114 47 35 30</td>
</tr>
<tr>
<td>8</td>
<td>27/F</td>
<td>57-kb del/ND</td>
<td>17</td>
<td>P, A, C</td>
<td>10</td>
<td>61 61 58 64 110 114 43 29 13</td>
</tr>
<tr>
<td>9</td>
<td>29/M</td>
<td>Q128X/Q128X</td>
<td>12</td>
<td>P, A</td>
<td>5</td>
<td>78 79 77 75 98 126 — — —</td>
</tr>
<tr>
<td>10</td>
<td>31/F</td>
<td>57-kb del/57-kb del</td>
<td>5</td>
<td>P, A</td>
<td>12</td>
<td>81 86 93 146 136 80 — 78 55</td>
</tr>
<tr>
<td>11</td>
<td>36/F</td>
<td>57-kb del/57-kb del</td>
<td>11</td>
<td>P, A</td>
<td>0</td>
<td>63 67 65 67 103 108 — — —</td>
</tr>
<tr>
<td>12</td>
<td>40/M</td>
<td>57-kb del/57-kb del</td>
<td>10</td>
<td>P, A</td>
<td>1</td>
<td>43 40 50 62 125 76 44 24 23</td>
</tr>
<tr>
<td>Mean</td>
<td>28</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>15</td>
<td>9 144 94 41 40 26</td>
</tr>
<tr>
<td>SEM</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>7 5 7 5</td>
</tr>
<tr>
<td>Ocular cystinosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>20/F</td>
<td>G197R/57-kb del</td>
<td>—</td>
<td>—</td>
<td>86</td>
<td>94 82 82 100 87 — — —</td>
</tr>
<tr>
<td>14</td>
<td>21/F</td>
<td>G197R/ND</td>
<td>—</td>
<td>—</td>
<td>97</td>
<td>111 85 56 65 104 — — —</td>
</tr>
<tr>
<td>15</td>
<td>26/M</td>
<td>I69R/splice</td>
<td>—</td>
<td>—</td>
<td>108</td>
<td>118 119 149 125 103 — — —</td>
</tr>
</tbody>
</table>

*del = deletion; ND = not determined; Tx = first renal transplant; P = prednisone; A = azathioprine; C = cyclosporine; MEA = mercaptoethylamine or cysteamine; M = male; F = female; D/VA = diffusing capacity for carbon monoxide adjusted for lung volumes.
progression to more widespread involvement of muscles. The EMG of patient 11 was suggestive of a sensory motor polyneuropathy. However, the EMG report noted that some features of a primary muscle disease in the distal hand muscles may have been overshadowed by the effect of the sensorimotor neuropathy. For patient 12, a limited EMG examination provided evidence for irritability of the biceps and intercostal muscles, typical of the primary muscle disorder seen in nephropathic cystinosis.

Muscle-related enzyme levels were normal in the sera of all patients, a finding typical for the distal vacuolar myopathy of cystinosis. A myopathy score (see "Materials and Methods" section) was assigned to each patient based on the clinical and electrophysiologic evidence for a primary muscle disease, combined with signs and symptoms of swallowing difficulty (Table 3). To correlate this score (0, +, or ++) with pulmonary function, the mean values of FVC, FEV₁, and TLC, as a percentage of predicted, were calculated for each patient. The extent of pulmonary dysfunction correlated directly with the severity of myopathy in our 12 patients (Fig 3).

Table 2—Absolute Values for MVV, MIP, and MEP in Cystinosis Patients*

<table>
<thead>
<tr>
<th>Patient No./Sex</th>
<th>MVV, L/min†</th>
<th>MIP, cm H₂O</th>
<th>MEP, cm H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>20</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>2/F</td>
<td>34</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>3/F</td>
<td>64</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td>6/M</td>
<td>41</td>
<td>39</td>
<td>79</td>
</tr>
<tr>
<td>7/M</td>
<td>55</td>
<td>45</td>
<td>72</td>
</tr>
<tr>
<td>8/F</td>
<td>44</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>10/F</td>
<td>—</td>
<td>69</td>
<td>85</td>
</tr>
<tr>
<td>12/M</td>
<td>43</td>
<td>29</td>
<td>53</td>
</tr>
</tbody>
</table>

Normal values ± SD‡
M 127±28 216±45
F 91±25 138±39

*See Table 1 for abbreviations.
†Test length = 12 s; normal values are 35 × FEV₁.
‡For patients from 19 to 49 years old.

A myopathy score (see "Materials and Methods" section) was assigned to each patient based on the clinical and electrophysiologic evidence for a primary muscle disease, combined with signs and symptoms of swallowing difficulty (Table 3). To correlate this score (0, +, or ++) with pulmonary function, the mean values of FVC, FEV₁, and TLC, as a percentage of predicted, were calculated for each patient. The extent of pulmonary dysfunction correlated directly with the severity of myopathy in our 12 patients (Fig 3).

Individual case histories are illustrative. Patient 1 received a living related donor renal allograft at the age of 6 years and was referred to the National Institutes of Health for muscle weakness at age 18 years. At this time, she was noted to have upper-extremity wasting (Fig 2, top) and weakness bilaterally, worse peripherally and with dorsiflexion or extension. Deep tendon reflexes were normal or slightly decreased. A swallowing study demonstrated significant weakness of facial muscles, with left palatal weakness and difficulty in manipulating a bolus. An oral sensory motor evaluation revealed mild to moderate difficulties in vocal quality, with soft and hypernasal speech and weakness. Sustained phonation was < 3 s in duration. A modified barium swallow revealed moderately delayed initiation of the pharyngeal swallow with piecemeal deglutition and bolus transport via gravity. An EMG revealed a muscle disorder involving the upper-extremity, facial, intercostal, and diaphragmatic muscles. Use of the intercostal muscles was observed even during quiet breathing. The patient began receiving cysteamine therapy at a dose of 500 mg free base every 6 h, with variable compliance over the next 3 years, during which time she maintained her weight at 38 kg. However, at age 21 years, her weight fell to 28 kg due to diarrhea and inability to swallow. An operative jejunostomy was placed, and she gained 7 kg. The patient developed atelectasis and died of respiratory failure 3 months later.

Patient 12 received a cadaveric renal transplant at the age of 10 years and one of his father’s kidneys at the age of 18 years. Hand strength deteriorated in his 20s, and swallowing worsened at approximately the age of 32 years. At age 36 years, he developed dyspnea on exertion and required oxygen at night. This patient had never received cysteamine therapy.
until his initial admission to the National Institutes of Health at the age of 39 years. At that time, motor strength was diffusely decreased, with generalized muscle atrophy (Fig 2, bottom) and abnormal pulmonary function test results. A chest radiograph showed atelectasis at the left base. At the age of 40 years, pulmonary function test results (Table 1) were unchanged, but the patient had a dry cough and clubbing of his fingers and required bilevel pressure ventilation at night to regulate his breathing pattern. There were no fasciculations noted, the cranial nerves were intact, and deep tendon reflexes were brisk in all extremities. The patient's speech was characterized by poor articulation, high pitch, and low volume. On swallowing evaluation, the patient could not handle a 20-mL bolus of water due to poor lip seal and prematurely swallowed a 10-mL bolus of water. There was a mild delay in initiation of swallowing, mild to moderate lingual pumping, and mildly slow movement of the hyoid bone. Esophageal motility and velopharyngeal movement were moderately impaired, and there was moderate weakness of the tongue and lips. The gag reflex was difficult to elicit. Ten months after his hospital admission, the patient developed aseptic necrosis of both hips and, while awaiting surgery, acquired an aspiration pneumonia and died just prior to his 41st birthday.

Lung tissue was not available from any of our 12 patients. Autopsy pulmonary tissue from a 7-year-old girl with nephropathic cystinosis who was never treated with cysteamine had birefringent, needle-like hexagonal and rectangular cystine crystals only occasionally visible with polarized light (Fig 4). No interstitial fibrosis or inflammation was seen.

**Discussion**

By investigating 12 cystinosis patients after renal transplantation, we found that significant pulmonary dysfunction occurs commonly in adults with this disease who have not received lifelong cysteamine therapy. For 2 of the 12 patients, the respiratory insufficiency proved fatal at 21 years of age and 40 years of age, respectively. The pulmonary dysfunction did not appear to be associated with renal disease, specific immunosuppressive medications, or a particular mutation of the CTNS gene (Tables 1, 3).

Impairment of pulmonary function also did not appear to be caused by lung parenchymal involvement. Specifically, chest radiographs and CT scans of our patients were essentially normal, with conspicuous absence of fibrosis or alveolar disease. The only circumstantial evidence for pulmonary parenchymal disease in cystinosis involves the occasional presence

---

**Table 3—Clinical, Genetic, and Myopathic Features of Cystinosis Patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Height (cm)†</th>
<th>Creatinine (mg/dL)</th>
<th>Muscle Disease</th>
<th>EMG</th>
<th>Speech</th>
<th>Swallowing</th>
<th>Myopathy Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>149</td>
<td>0.3</td>
<td>Severe wasting, weakness</td>
<td>Muscle disorder</td>
<td>Hypophonic, hypernasal</td>
<td>Reflux, delayed</td>
<td>+ +</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
<td>1.3</td>
<td>Hand muscle weakness</td>
<td>ND</td>
<td>Hypophonic</td>
<td>Reduced peristalsis</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>143</td>
<td>1.3</td>
<td>Subtle weakness</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>131</td>
<td>1.3</td>
<td>Mild weakness all extremities</td>
<td>ND</td>
<td>Mildly hypophonic</td>
<td>Impaired tongue motion</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>135</td>
<td>1.0</td>
<td>Normal</td>
<td>ND</td>
<td>Normal</td>
<td>Mild esophageal dysmotility</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>141</td>
<td>1.1</td>
<td>Atrophy of hand muscles</td>
<td>Distal myopathy</td>
<td>Hypophonic, hypernasal</td>
<td>Impaired tongue motion and swallow</td>
<td>+ +</td>
</tr>
<tr>
<td>7</td>
<td>147</td>
<td>4.9</td>
<td>Neck flexor weakness</td>
<td>ND</td>
<td>Normal</td>
<td>Delayed peristalsis</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>150</td>
<td>0.8</td>
<td>Hand, arm muscle atrophy</td>
<td>Muscle disease</td>
<td>Hypophonic, hypernasal</td>
<td>Delayed initiation and peristalsis</td>
<td>+ +</td>
</tr>
<tr>
<td>9</td>
<td>167</td>
<td>0.9</td>
<td>Normal</td>
<td>Hand myopathy</td>
<td>Normal</td>
<td>Trace deficits</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>128</td>
<td>4.2</td>
<td>Atrophy of hand muscles</td>
<td>ND</td>
<td>Hypophonic</td>
<td>Delayed initiation</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>146</td>
<td>0.7</td>
<td>Normal</td>
<td>Primary hand muscle disease</td>
<td>Normal</td>
<td>Esophageal dysmotility</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>140</td>
<td>1.3</td>
<td>Severe, generalized wasting</td>
<td>Irritable biceps and intercostals</td>
<td>Hypophonic, hypernasal</td>
<td>Delayed initiation esophageal dysmotility</td>
<td>+ +</td>
</tr>
</tbody>
</table>

* 0 = very mild muscle weakness or swallowing difficulty; + = moderate muscle weakness or atrophy on physical examination; ++ = severe wasting and weakness involving the arms and shoulders, with moderate to severe impairment of swallowing. See Table 1 for other abbreviation.

† Normal heights for adult men are 166 to 188 cm, normal heights for adult women are 154 to 174 cm.
of crystals within the lung itself. We were able to identify cystine crystals in a postmortem specimen of lung from a 7-year-old girl with nephropathic cystinosis who had never received cystine depletion therapy (Fig 4). Cystine crystals have also been reported in macrophages surrounding a pulmonary blood vessel and in “pneumocytes.” However, the mere presence of cystine crystals in cystinosis tissue does not signal dysfunction; the liver, spleen, and intestine of cystinosis patients are packed with crystals, yet there is no significant functional impairment of these tissues.

Rather than resulting from lung parenchymal disease, our patients’ pulmonary insufficiency was apparently caused by extraparenchymal restriction of ventilation. Airflow rates, as determined by spirometry and lung volumes, were significantly reduced despite near-normal diffusing capacities. One possible extraparenchymal cause would be a conical chest configuration, found in 7 of 12 patients. This finding probably resulted from rickets and growth impairment early in life, which could limit chest excursion and reduce maximal lung volumes.

A more likely suspect for causing pulmonary dysfunction in cystinosis, however, is the muscle wasting and weakness characteristic of this disease. The wasting has been demonstrated to represent muscle disease rather than nerve involvement. Specifically, it is characterized by type 1 fiber atrophy, cystine crystal accumulation in perimysial cells, and formation of intracellular vacuoles. It resembles the distal vacuolar myopathy of acid maltase defi-
other tissues

therapy lowers the cystine content of muscle and
clearance. The profound reduction in MVV,
reduced MVV indicated decreased respiratory mus-
cles within alveolar macrophages and the interstitium in pulmo-
occasionally included the accessory muscles of the
chest, and pulmonary function test results supported

Our conclusion was that restrictive pulmonary disease
are due to respiratory muscle dysfunction is part of the
natural history of nephropathic cystinosis not treated
from infancy with oral cysteamine. Consequently, it
is important to evaluate adult cystinosis patients for
respiratory function. Oral cysteamine currently of-

We conclude that restrictive pulmonary disease
due to respiratory muscle dysfunction is part of the
natural history of nephropathic cystinosis not treated
from infancy with oral cysteamine. Consequently, it
is important to evaluate adult cystinosis patients for
respiratory function. Oral cysteamine currently of-

Ten of our 12 patients had significant clinical or
electrophysiologic evidence of a myopathy (Table 3). Often the muscle atrophy was apparent on inspec-
tion (Fig 1), and in two occasions it led to death due to respiratory insufficiency. The myopathic findings
occasionally included the accessory muscles of the chest, and pulmonary function test results supported
this finding. Reduced values of MIP and MEP were observed in all eight patients tested (Table 2), indicat-
ing decreased respiratory muscle strength; the reduced MVV indicated decreased respiratory muscle
endurance. The profound reduction in MVV, MIP, and MEP is consistent with a myopathic cause for the
restrictive ventilatory impairment in the study population. Furthermore, the mean value for three
routine pulmonary function tests (FVC, FEV₁, and TLC, expressed as a percentage of predicted) corre-
lated directly with the myopathy score in our 12

A critical issue regarding pulmonary dysfunction
in cystinosis is whether it can be treated or prevented
with oral cysteamine therapy. Based on cross-sectional studies of cystinosis patients at different ages,
we expect that cystine accumulation was progressive in each of our 12 patients for at least 17
years (mean, 24 years; maximum, 39 years), since they had been without effective cysteamine therapy
for that long. Cysteamine can deplete cultured muscle
cells of cystine, and long-term oral cysteamine therapy lowers the cystine content of muscle and other tissues in vivo. Therefore, this treatment

Fig 4. Birefringent hexagonal and rectangular cystine crys-
tals within alveolar macrophages and the interstitium in pulmo-

Clinical Investigations

References

1 Gahl WA, Schneider JA, Aula P. Lysosomal transport disor-
ders: cystinosis and sialic acid storage disorders. In: Scriver
CR, Beaudet AL, Sly WS, et al, eds. The metabolic and
molecular bases of inherited disease. 7th ed. New York, NY:
McGraw-Hill, 1995; 3763–3797
33:95–126
from isolated lysosome-rich fractions of cystinotic leukocytes.
J Biol Chem 1982; 257:9570–9575
4 Gahl WA, Bashan N, Tietze F, et al. Cystine transport is
defective in isolated leukocyte lysosomes from patients with
cystinosis. Science 1982; 217:1263–1265
5 Jonas AJ, Smith ML, Schneider JA. ATP-dependent lysoso-
mal cystine efflux is defective in cystinosis. J Biol Chem 1982;
257:13185–13188
cystine depletion by aminothiols in vitro and vico. J Clin
Invest 1976; 58:180–189
7 Gahl WA, Reed GF, Thoene JG, et al. Cysteamine therapy
316:971–977
8 Markello TC, Bernardini IM, Gahl WA. Improved renal
function in children with cystinosis treated with cysteamine.

Kaiser-Kupfer MI, Fujikawa I, Kuwabara T, et al. Removal of
corneal crystals by topical cysteamine in nephropathic
11 Kaiser-Kupfer MI, Gazzo MA, Datiles MB, et al. A random-
ized placebo-controlled trial of cysteamine eye drops in
693
adult. JAMA 1957; 164:394–396
13 Anikster Y, Shotelersuk V, Gahl WA. CTNS mutations in
patients with cystinosis. Hum Mutat 1999; 14:454–458
37 Barohn RJ, McVey AL, DiMauro S. Adult acid maltase deficiency. Muscle Nerve 1993; 16:672–676