Many neurologic symptoms occur with coughing paroxysms in patients with CF. Few seek medical advice for these symptoms. Rarely, a patient who reports these symptoms should be evaluated further for more serious neurologic conditions, including brain abscess.[12] However, for most patients it seems reasonable to offer reassurance that, although the symptoms may be alarming, the incidence of irreversible sequelae appears small.

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Neurologic and cognitive deficits in children with cystinosis

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Infantile nephropathic cystinosis becomes clinically apparent in the first year of life, usually with failure to thrive and signs of renal tubular dysfunction. In children, photophobia, chronic renal failure, and hypothyroidism develop. Pathologic studies demonstrate deposition of cystine crystals in many tissues, including cornea, kidney, thyroid gland, choroid plexus, and, rarely, brain parenchyma.[1-3]

Supported in part by grant No. PHS RR-00827 from the General Clinical Research Branch, Division of Research Resources, National Institutes of Health, by grant No. DK-18434 from the National Institutes of Health, and by Center grant No. PHS NS-22343-02 from the National Institutes of Health. Also supported by gifts from the B. L. Maas Foundation and the Cystinosis Foundation.

Submitted for publication May 26, 1987; accepted Jan. 13, 1988.

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Radiologic evidence of both cerebral atrophy and communicating hydrocephalus has been found in a few children.[2,4] Except for occasional reports of seizures, there has been little indication of clinical neurologic problems.[5] Overall IQ scores tend to be normal, and school performance is reported to be average.[6,7] Jonas et al.[8] reported intellectual deterioration in one adult.

We performed neurologic, ophthalmologic, and neuropsychologic testing on patients with cystinosis. We used unaffected siblings as control subjects and patients with chronic renal failure from other causes as a contrasting "disease control" group.

METHODS

Twenty-two patients with cystinosis, 12 unaffected siblings, and eight subjects with chronic renal failure from other causes were studied. Patients with cystinosis all had a typical history and laboratory confirmation of infantile nephropathic cystinosis. Age range was 2.9 to 28.5 years in

Table. Performance of cystinosis patients, unaffected siblings, and children with renal failure on selected subtests of the Stanford-Binet Intelligence Scale, Fourth Edition

Subtest	Cystinosis (n = 18)	Siblings (n = 12)	Renal (n = 6)
Vocabulary	51.0 ± 5.6	48.8 ± 5.5	49.0 ± 9.1
Pattern Analysis	49.4 ± 6.6	51.7 ± 6.1	39.3 ± 5.2†
Quantitative Analysis	49.5 ± 7.3	49.4 ± 6.1	44.5 ± 9.0
Bead Memory	43.3 ± 5.2*	49.0 ± 9.0	38.8 ± 6.9‡
Memory for Sentences	52.5 ± 7.3	54.8 ± 7.0	41.2 ± 12.7
Composite	97.6 ± 9.8	101.3 ± 11.3	83.5 ± 15.3§

See text for details of statistical analyses.
*p <0.05 compared with siblings.
†p <0.001 compared with norms for age.
‡p <0.02 compared with norms for age.
§p <0.02 compared with cystinosis patients and siblings.

cystinosis patients (mean 11.7 years), 2.6 to 27 years in siblings (mean 12.5 years) and 3.1 to 20 years in patients with renal failure (mean 14.0 years). The sex ratio was approximately equal for all groups. Seven patients with cystinosis had had renal transplants; 12 others were receiving long-term treatment with cysteamine.[9,10]

Patients with renal failure were chosen on the basis of age and absence of complicating features such as episodes of coma, status epilepticus, or hypertensive encephalopathy. Causes of their renal disease included systemic lupus erythematosus, glomerulonephritis, congenital anomaly of the kidney, and hydronephrosis caused by uncomplicated sacral meningomyelocele.

After informed consent was obtained, 40 subjects had a neurologic examination (two adults with cystinosis were not examined). Each cystinosis patient had an ophthalmologic evaluation, which included slit-lamp biomicroscopy and dilated funduscopy. Five subtests of the Stanford-Binet Intelligence Test, Fourth Edition, were given to all subjects except for two adults with cystinosis and visual impairment, one Spanish-speaking child, and one adult with cystinosis and two renal failure patients who could not complete the test. The subtests were Vocabulary, Pattern Analysis, Quantitative Analysis, Bead Memory, and Memory for Sentences. These subtests were chosen because they represented the four major divisions of the test: Verbal Reasoning, Abstract/Visual Reasoning, Quantitative Reasoning, and Short-Term Memory. Bead Memory and Memory for Sentences subtests were both used to test visual and auditory short-term memory, respectively. The Stanford-Binet test is standardized by age from two years to adulthood.

Statistical procedures used were the Student t test, analysis of variance, and Student-Newman-Keuls multiple range test.

RESULTS

Neurologic deficits. Neurologic deficits were found in most subjects with cystinosis. One 25-year-old man had severe impairment with encephalopathy, rigidity, tremor, and gait apraxia. He had developed progressive dysfunction over 5 years, after having been a normally functioning person with some college education. No antecedent events other than cystinosis accounted for his problems. Eleven of twenty patients had marked generalized hypotonia. Five of twenty had an intention tremor. Eight of seventeen patients whose head measurements were recorded had a head circumference less than the 10th percentile for age, and two had less than the third percentile. Sixteen of twenty patients had impaired gross and fine motor skills. Three young children had speech delay.

Of the siblings, one had visual motor deficits and learning disabilities. No other overt neurologic impairments were found.

Three patients with renal failure had mild diffuse hyperreflexia, one with meningomyelocele had distal atrophy and decreased sensation in the legs, and one had global psychomotor retardation. In three of five patients, recorded head circumference was at or below the tenth percentile for age. No abnormalities of muscle tone and no tremors were found in this group.

Ophthalmologic findings. Two adult patients with cystinosis had significant visual impairment (<20/200). All others had normal visual acuity (≥20/40) with intact color vision. All had the classic anterior segment findings of cystinosis, with crystal deposition in the conjunctiva and cornea. Ocular motility testing showed no deficits. Stereo acuity was intact. No patient had nystagmus or other adventitial eye movements. Funduscopy revealed depigmentation of the peripheral retina with alteration of the retinal pigment epithelium in all patients. Each fundus had

a mottled appearance, in a patchy distribution, from mid-equator to the ora serrata retinae. Optic nerves were of normal color, contour, and capillarity. No abnormality of nerve fiber layer was found.

Cognitive findings. Composite IQ scores of cystinosis patients were normal (97.6 ± 9.8; range 74-118). All subtest scores (Table) were in the normal range, except for scores on the Bead Memory subtest, which were significantly below the norm (43.3 ± 5.2 vs expected norm 50; $p < 0.001$). Newman-Keuls comparisons between subtests revealed only scores on the Bead Memory subtest to be significantly lower ($p < 0.01$) than other subtest scores.

Test comparisons between patients who had renal transplants and those treated with cysteamine showed no significant differences (composite IQ 94.8 ± 5.6 for transplant patients vs 99.4 ± 11.1 for cysteamine-treated patients; Bead Memory 41.3 ± 5.5 vs 43.7 ± 5.7).

Mean composite IQ scores of siblings were 101.3 ± 11.3, demonstrating no difference from their siblings with cystinosis. Siblings scored in the normal range on all subtests; their performance on the Bead Memory subtest was significantly better than the performance of those with cystinosis ($p < 0.05$).

The IQ scores of patients with renal failure were lower than average (83.5 ± 15.3) and lower than scores for the cystinosis group ($p < 0.02$; Table). No specific deficit was found; they appeared to have global cognitive difficulties. Newman-Keuls comparisons revealed no significant differences among subtest scores within the renal failure group.

DISCUSSION

Our results suggest that cystinosis does not spare the central nervous system. The majority of patients have neurologic deficits, primarily motor incoordination and hypotonia. Progressive neurologic dysfunction may occur in young adults.

We also observed that despite normal intelligence, patients with cystinosis have an apparently isolated deficit in short-term visual memory. This deficit was not demonstrated in the group of unaffected siblings. The overall IQ scores for cystinosis patients and their siblings were virtually identical, so the visual memory deficit cannot be explained by a generalized deficiency in cognitive ability. Careful ophthalmologic evaluation revealed no ocular cause for this defect. Chronic renal failure does not seem to explain the problem, because patients with renal failure from other causes did not have any specific deficit. Cysteamine treatment does not appear to be the cause of the impairment, because 10 of the patients had not received cysteamine. Although the number of patients with cystinosis in our study who had undergone renal transplantation was small, there was no significant difference in their performance on the visual memory task compared with those who had been treated with cysteamine.

The cause of the observed visual memory deficit is not clear. The deficit may not be specific but, rather, may be a function of the test employed (i.e., the Bead Memory test may merely be more sensitive to central nervous system impairment than other tests used in the study). Alternatively, it is conceivable that certain neuronal populations (i.e., those involved in visual memory) are more susceptible to cystine accumulation. Analysis of regional neuropathologic changes, careful neuroimaging studies, and more extensive neuropsychologic testing may help to clarify these issues.

We thank Dr. Stanley Mendoza for identifying control patients with renal failure for our study, and Mrs. Ana Ney for her invaluable assistance in coordinating patient testing and data acquisition forms. We also thank the children and adults with cystinosis and their families for giving their time to participate in the study.

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