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Effect of Age of Treatment on Cognitive Performance in Patients with Cystinosis

Lisa Viltz, B.S.¹ and Doris A. Trauner, M.D.^{1,2,3}

¹Department of Neurosciences, UCSD School of Medicine, La Jolla CA USA

²Department of Pediatrics, UCSD School of Medicine, La Jolla CA USA

³Rady Children's Hospital San Diego

Abstract

Objectives—To determine whether early treatment with cysteamine affects cognitive functioning in patients with nephropathic cystinosis.

Study design—Individuals (n = 46, ages 3–18 years) with cystinosis underwent cognitive testing to determine intelligence, visual spatial abilities, and visual motor skills. An age-matched control group (n = 85, age range 2–22 years) received the same tests. Age at diagnosis and age at treatment onset with cysteamine were recorded at the time of testing.

Results—Patients with cystinosis treated at or after 2 years of age (late-treatment patients) scored significantly lower on verbal, performance, and full-scale IQ measures, as well as on a test of visual spatial skills when compared to early treatment patients (treatment onset <2years old) and to controls. Regardless of the age of treatment, both groups of subjects with cystinosis showed impairment in visual motor skills compared with controls; early-treatment patients showed no advantage in this area.

Conclusion—Early treatment with cysteamine appears to improve intellectual function in nephropathic cystinosis. However, the fact that visual motor function was not improved with early cysteamine treatment suggests that the mechanisms underlying visual motor performance may be different from other areas of cognition in this disorder.

Keywords

cysteamine; cognitive function

Nephropathic cystinosis is an autosomal recessive disorder that occurs in approximately 1 per 100,000 live births¹. The defect has been mapped to a mutation in chromosome 17p13, which encodes the lysosomal membrane transport protein cystinosin (CTNS). Multiple mutations have been identified, most leading to the inactivation of the cystinosin protein^{2–3}. With the inactivation of CTNS, the amino acid cystine is incapable of crossing the

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Address correspondence to: Doris A. Trauner M.D., Department of Neurosciences, UCSD School of Medicine, 9500 Gilman Drive, MC 0935, La Jolla, CA 92093-0935, Telephone 858-822-6800, Fax 858-822-6707, dtrauner@ucsd.edu.

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lysosomal membrane, causing accumulation of cystine crystals in virtually all organs, including the brain¹.

The kidney is the first organ affected by the disease, usually within the first 6 to 12 months of life. Other complications arise over time. These may include thyroid dysfunction, growth retardation, progressive visual impairment, pancreatic dysfunction¹, myopathy⁴, and in rare cases, dementia⁵⁻⁶.

Treatment with cysteamine (beta-mercaptoethylamine, MEA) generally begins as soon as the diagnosis is made. This medication effectively decreases the rate of cystine buildup within cells¹. Life expectancy has increased markedly and quality of life is significantly improved with cysteamine treatment⁷.

Collective data from MRI scans, CT scans, and autopsies has revealed that cystinosis is associated with altered brain structure and increased levels of cystine in many areas of the brain⁸⁻¹². Despite the structural changes in the brains of patients with cystinosis, neurological and cognitive changes have generally been relatively mild. Patients with the disease fall within the range of normal intelligence and have normal language, verbal learning, and reading skills¹³⁻¹⁵. The primary cognitive deficits in patients with cystinosis are in visuospatial abilities, visual motor coordination, and short-term visual memory. Neurological difficulties consist primarily of impaired gross and fine motor skills and seizures¹⁴⁻²⁰. Patients with cystinosis may experience academic challenges, especially in spelling and math¹⁵.

The underlying cause of the cognitive impairments is not clear. One possible explanation is that progressive cystine accumulation in the brain over time causes functional as well as structural damage. If this is the case, then early treatment with cysteamine should reduce cognitive deficits. The present study was conducted to examine whether early treatment with cysteamine was associated with more favorable cognitive outcomes.

Methods

Forty-six children and adolescents with nephropathic cystinosis ages 3 through 18 years (mean age, 7.3 ± 4.5 years) participated in the study. This testing was part of a larger, longitudinal study of brain structure and function in cystinosis. Each participant was diagnosed by his or her nephrologist with nephropathic cystinosis, based on clinical presentation and by assays documenting elevated leukocyte cystine concentrations. Patients with other medical issues (ie, untreated thyroid dysfunction, uncorrected vision problems, and patients in renal failure) were excluded, as these factors may adversely affect cognitive performance. Individuals were also excluded if they were on dialysis, were acutely ill, or had any other condition that might adversely affect cognitive function. Only one subject was excluded for these reasons.

Subjects were recruited at family conferences organized by one of the cystinosis foundations (Cystinosis Research Network, Cystinosis Research Foundation and Cystinosis Foundation). Individuals were recruited from around the country, and either traveled to San Diego for testing, or were tested while attending the family conferences. Background and demographic information was obtained on each participant, including the age at start of treatment with cysteamine. On the basis of this information, subjects were divided into early treatment (prior to or by the age of 2 years) or later treatment (after the age of 2 years) for later analyses. The rationale for choosing 2 years as a cutoff for “early” vs. “late” treatment is that many children are not diagnosed until at least 12–18 months of age and so treatment is often not instituted prior to about 2 years of age²¹.

We were unable to acquire specific information about renal function on most of the patients for various reasons. However, some of these children participated in another study at the same time as ours, and all had estimated glomerular filtration rates (eGFRs) between 79 and 122 mL/min per 1.73 m² or stage 1 or 2 kidney disease²².

A control group consisting of 85 individuals ages 2 through 22 (mean age, 8.3 ± 4.8 years) was used for comparison. Controls were group-matched to subjects with cystinosis on the basis of age and socio-economic status. All control participants were free of neurological, psychiatric and developmental problems, and did not have any other underlying condition that might affect cognitive function. Control subjects were recruited through IRB-approved advertisements in local parent magazines, through flyers placed in pediatricians' offices, and through the UCSD subject pool. For all subjects, informed consent was obtained from the parent and/or subject prior to testing, as well as an assent from children over the age of 7 years, in accordance with UCSD Human Subjects Protection Program policies.

Intelligence was measured using an age-appropriate Wechsler Intelligence Scale. These tests are well normed and have a mean of 100 and standard deviation of 15^{23–25}.

The Spatial Relations Test from the Woodcock-Johnson Psychoeducational Battery²⁶ was used to measure visual spatial ability. This test does not require motor involvement. Subjects were shown pictures containing a series of shapes from which they were required to select component parts in order to make a whole. Raw scores were converted to standard scores with a mean of 100 and a standard deviation of 15. This test is normed for 2 years of age and older.

Visual motor skills were measured with the Beery-Buktenica Developmental Test of Visual Motor Integration (VMI), 5th Edition²⁷. The VMI required each participant to copy a series of increasingly complex geometric figures. Raw scores were converted to standard scores with a mean of 100 and a standard deviation of 15. This test is also normed for 2 years of age and older.

Data Analyses

Multivariate Analysis of Variance techniques were used to compare early- and late-treated subjects with cystinosis with controls on VIQ, PIQ and FS IQ. Post-hoc independent-sample t-tests were performed using SPSS statistical analysis software. For Spatial Relations and VMI tasks, analysis of variance was used to compare early- vs. late-treatment cystinosis groups.

Results

Individuals with cystinosis in the early-treatment group scored significantly higher on performance IQ testing than did the subjects in the late-treatment group. Both groups were significantly lower than controls on all IQ measures. Importantly, however, the scores of the early-treatment group, despite being lower than the controls, still fell within the normal range, whereas the late-treatment mean scores were below the normal range for PIQ and in the low normal range for FSIQ (Table). Scores on the Spatial Relations test were within the normal range for both treatment groups, although the late-treated group scored significantly lower than the early treated group (Figure).

An analysis of selected subtest scores for Performance IQ measures further demonstrated a pattern of overall poorer performance by the children with cystinosis compared with controls (Table). Scores on the Block Design subtest, a spatially mediated task, were significantly lower in the late-treatment than the early-treatment group, whereas scores on

the Picture Completion subtest, which assesses visual perception, were not significantly different between the two cystinosis groups.

There were no significant differences between early and late treatment groups on the test of visual motor ability, with both groups scoring well below the expected mean. The mean for the late-treatment group fell more than one standard deviation below the normal range, however. There were also no significant differences between the cystinosis groups on another task of speeded motor function, the Symbol Search subtest, with both groups scoring well almost one standard deviation below the expected mean of 10.

Discussion

The introduction of cysteamine for the treatment of nephropathic cystinosis has made a remarkable impact on the disease. Multiple studies have demonstrated significant benefits of cysteamine with regard to preserved renal function, growth, and other systemic manifestations^{1,7}. Cysteamine treatment has also been shown to halt the progression of dementia that has been shown to develop in adults with cystinosis⁶. The current study documents a beneficial effect of cysteamine on cognitive function in children with cystinosis. Children with nephropathic cystinosis who were treated prior to 2 years of age had significantly higher scores on intelligence tests and on a test of spatial relations than did children treated after 2 years of age. Interestingly, however, visual motor skills did not benefit from early treatment, suggesting that the underlying mechanism by which visual motor skills are adversely affected in cystinosis may be different from those involved in other aspects of neuro-cognitive function.

The fact that early treatment results in preserved intellectual function in cystinosis suggests that the cognitive impairment may at least in part be due to progressive accumulation of cystine in the brain over the first years of life, during a crucial time in brain development. Cystine accumulation may have a destructive impact on myelination and other microstructural elements of white matter in the brain, which may lead to alterations in the development of fiber networks important for cognitive, motor, and sensory abilities. In fact, a recent study from our laboratory demonstrated abnormalities in white matter integrity in both parietal lobes of children with cystinosis²⁸. That finding, in conjunction with those of the current study, lends support to the hypothesis that early cystine accumulation may underlie some of the neuropathology of this condition. However, it is also possible that there is damage to other developing neural elements as a result of early cystine accumulation. Currently, the mechanism by which cystine damages cells is unknown, but it is reasonable to speculate, based on the current study, that introducing a cystine-depleting agent into the body as early as possible may afford the brain some protection against such injury.

An alternative explanation for the better cognitive performance of the early-treatment group relates to the impact of treatment on renal dysfunction. The natural history of untreated cystinosis is that of progressive renal failure ultimately requiring dialysis and eventually kidney transplant before the age of ten. If renal complications remain untreated over the first several years of life, a child's cognitive functioning may be adversely impacted due to progressive renal dysfunction²⁹. Reducing the severity of renal complications earlier may allow a child's brain to develop more normally. A limitation of the current study was the lack of information on the degree of renal damage prior to onset of treatment with cysteamine in our subjects. We also did not have information about renal function at the time of our testing, and although parents reported that their children's renal function was "acceptable" based on their personal physicians' reports, it is possible that different degrees of renal impairment were present between the two cystinosis groups. This would not, however, explain the differential performance on visual spatial vs. visual perceptual tasks,

because renal dysfunction is more likely to be associated with global cognitive deficits than with specific types of impairments²⁹.

Although the beneficial effect of early treatment on cognitive function is clearly demonstrated in the present study, some problems still remain. Specifically, visual motor skills are impaired in both the early- and late-treated cystinosis groups. It is possible that these are more complex tasks tapping several cognitive skills, and are able to reveal subtle persistent deficits that less complex tasks do not. It is also possible that the underlying cause of the visual motor deficit is different from that of general intellectual function. Given that visual motor dysfunction is evident even in young children after treatment²⁰, it is possible that either pre-natal cystine accumulation is responsible for such neurological changes, or that the gene itself exerts an as yet unknown effect on brain development. Further studies are needed to identify the precise mechanisms by which cystinosis produces aberrations in brain development. Whatever the ultimate mechanism, however, this study demonstrates the importance of early diagnosis and treatment of cystinosis in order to better preserve cognitive functioning in these individuals.

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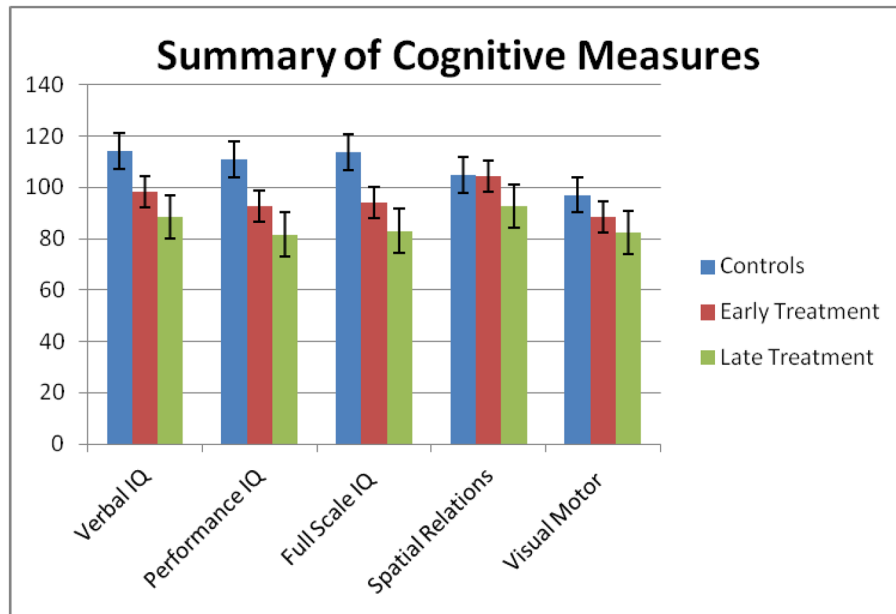


Figure. Comparison of scores on primary cognitive tests for controls, early-and late-treated patients with cystinosis (mean \pm standard error)

Table 1

Mean, standard deviation and p values of cognitive tests in individuals with cystinosis treated before or after age 2 years.

Cognitive Measure	Controls	Early-Treatment	Late-Treatment	P value*
Verbal IQ	114.0 ± 14.8 n = 85	98.2 ± 11.1 n = 32	88.6 ± 15.2 n = 14	.022
Performance IQ	110.8 ± 13.2 n = 85	92.7 ± 15.3 n = 32	81.6 ± 13.2 n = 14	.023
Full Scale IQ	113.6 ± 13.2 n = 85	94.0 ± 12.5 n = 32	83.0 ± 15.1 n = 14	.013
Spatial Relations	104.7 ± 16.1 n = 81	104.5 ± 12.0 n = 29	92.7 ± 22.6 n = 11	.038
Visual Motor (VMI)	97.1 ± 13.2 N = 81	88.5 ± 17.5 n = 30	82.3 ± 13.1 n = 11	NS
Picture Completion	11.43 ± 2.92 n = 75	9.04 ± 3.49 n = 27	7.18 ± 3.43 n = 11	.144
Block Design	12.45 ± 3.26 n = 82	8.88 ± 2.91 n = 33	6.71 ± 3.56 n = 14	.035
Symbol Search	12.33 ± 2.88 n = 75	7.85 ± 2.64 n = 27	7.09 ± 2.39 n = 11	.414

* Statistical comparisons of Early- vs. Late-Treatment groups.

p values for cystinosis groups compared with controls were all <.001.