

Academic Achievement in Individuals With Infantile Nephropathic Cystinosis

Angela O. Ballantyne, Kathleen M. Scarvie, and Doris A. Trauner*

Departments of Neurosciences and Pediatrics, University of California, San Diego, School of Medicine, La Jolla, California

The present study examined academic skills in children and young adults with infantile nephropathic cystinosis. Cystinosis is a genetic metabolic disorder in which the amino acid cystine accumulates in various tissues and organs, including the kidney, cornea, thyroid, and brain. Individuals with cystinosis have normal intelligence but subtle visual processing impairments. Subjects were 19 children and young adults with cystinosis and 19 age-, sex-, and IQ-matched controls. All subjects had IQs within the normal range. On a test of academic achievement, mean standard scores for cystinosis and control subjects, respectively, were as follows: arithmetic 89.95 ± 13.77 vs. 102.16 ± 9.62 ; spelling 90.68 ± 18.81 vs. 98.00 ± 10.96 ; reading 97.47 ± 15.59 vs. 98.58 ± 12.41 . Multivariate analysis of variance revealed a significant main effect for Group ($P = .009$); there was no main effect for Sex, nor was there a Group x Sex interaction. Univariate follow-up tests indicated that the cystinosis group performed significantly more poorly than did controls on the arithmetic subtest ($P = .001$) and that there was a trend ($P = .085$) toward poorer performance by the cystinosis group on the spelling subtest. Regression analyses revealed no evidence of a developmental lag or deterioration of function with age. The visual processing deficits previously identified in these individuals may underlie the academic difficulties observed here. It is possible that both visual processing and academic difficulties may reflect a common mechanism of selective cortical damage by this genetic defect. *Am. J. Med. Genet.* 74:157-161, 1997.

© 1997 Wiley-Liss, Inc.

KEY WORDS: cystinosis; WRAT-R; visual processing; autosomal recessive; neurogenetics

INTRODUCTION

Cystinosis is an autosomal recessive metabolic disorder characterized by defective transport of the amino acid cystine out of lysosomes, and consequent cystine deposition in various tissues and organs of the body including the kidney, cornea, and thyroid. There is also evidence of increased brain levels of cystine in children and adults with cystinosis [e.g., Ebbesen et al., 1976; Jonas et al., 1987; Levine and Paparo, 1982; Vogel et al., 1990]. Studies of the cognitive effects of cystinosis suggest specific visual processing deficits against a background of normal intelligence [Nichols et al., 1990; Trauner et al., 1988, 1989; Wolff et al., 1989]. For example, individuals with cystinosis exhibit deficits on tasks involving complex visual processing and spatial relations, but maintain intact skills in the areas of auditory processing, auditory attention and memory, receptive language, and basic visual perception [Trauner et al., 1989; Nichols et al., 1990]. There are several potential mechanisms by which these cognitive deficits could occur. For example, early accumulation of cystine in the fetal brain could potentially alter brain development. Progressive accumulation of cystine in postnatal life might cause later alterations in cognitive or neurologic function. It is possible that both of these mechanisms might be at work simultaneously.

Personal communications from affected families indicate that academic difficulties in individuals with cystinosis are a common concern, yet few studies have addressed this issue. Wolff et al. [1982] studied the psychosocial and intellectual development of 12 German children with cystinosis. They found school performance to be predominantly "average" or "normal" according to school records and teachers' impressions. No standardized measure was administered, however. Another study by Wolff et al. [1989] indicated that children with cystinosis had "average" school performance, though no formal assessment of such was apparent. Ehrich et al. [1979] studied four children with cystinosis, all of whom had documented brain atrophy on CT. Despite their brain atrophy, the children's school per-

Contract grant sponsor: National Institutes of Health; Contract grant number RO1 HD 23854; Contract grant sponsor: General Clinical Research Center; Contract grant number MO1 RR 00827.

*Correspondence to: Doris A. Trauner, M.D., Division of Pediatric Neurology, 0935, University of California, San Diego, La Jolla, CA 92093-0935. e-mail: dtrauner@ucsd.edu

Received 21 May 1996; Revised 26 August 1996

formance was "mainly average." Williams et al. [1994] studied intellectual and academic function in families affected by cystinosis and found that children with cystinosis had normal IQs, but that their IQs were significantly lower than those of their parents and siblings, suggesting an adverse effect of cystinosis on the nervous system. In addition, academic performance, particularly in spelling, was poorer in children with cystinosis than in their parents and siblings. The Williams et al. study, however, was specifically a family study (i.e., comparisons were made only among family members) and did not make comparisons to normal control children or to normative standards.

OBJECTIVE

The present study was undertaken to examine academic functioning, as assessed by the Wide Range Achievement Test-Revised (WRAT-R) [Jastak and Wilkinson, 1984], in individuals with cystinosis. The WRAT-R assesses academic skills in the areas of arithmetic, spelling, and reading. The performance of the cystinosis subjects was compared to that of individually-matched control subjects, as well as to the normative standards. In addition, the cystinosis subjects' academic performance at different ages was evaluated to determine whether or not there were changes in performance over time (e.g., improvement or decline). A change over time could be indicative of either a developmental lag or a deterioration of cognitive function, whereas no change over time would suggest a static deficit.

Normally developing controls were used as a contrasting group for several reasons. First, patients with cystinosis have previously been said to perform at normal levels in school, and they do not demonstrate severe cognitive or intellectual deficiencies. Since they are in age-appropriate classroom placements, the goal was to determine whether subtle academic differences might be present despite the placement. Second, no more suitable control group could be identified. For example, patients with other chronic medical conditions are inappropriate controls because of 1) invasive treatments that can affect the brain (e.g., radiation therapy for leukemia), 2) secondary neurologic complications of the disease (e.g., chronic hypoxemia in cystic fibrosis), or 3) potential primary neurologic or cognitive effects of the underlying medical condition (e.g., Turner syndrome).

In light of the anecdotal reports of academic difficulties, documented CNS involvement, and visual-spatial difficulties in individuals with cystinosis, it was hypothesized that they would demonstrate difficulty in at least some areas of academic achievement. In addition to further defining the neurocognitive effects of the disorder, the present study may have implications for remediation and ultimately for the academic success of children with this disorder. In addition, such studies may provide a better understanding of the behavioral consequences of genetic disorders.

METHODS

Subjects

Nineteen subjects with a diagnosis of infantile nephropathic cystinosis (9 males, 10 females), and 19 control subjects (9 males, 10 females) participated in the study. Control subjects were individually matched to the cystinosis subjects on the basis of age (± 1 year for subjects < 18 years, ± 3 years for subjects ≥ 18 years), sex, and IQ (± 10 points). Statistical analysis indicated that the groups did not differ on age (cystinosis group: mean age = 8 years 10 months, range = 5 years 1 month to 25 years 4 months; control group: mean age = 8 years 9 months, range = 5 years 1 month to 26 years 0 months) or IQ (cystinosis group: mean IQ = 108 ± 10 ; control group: mean IQ = 108 ± 9). All subjects had IQs within the normal range (≥ 85) and were free from uncorrected visual difficulties. The diagnosis of infantile nephropathic cystinosis was based on elevated leukocyte cystine levels [Smith et al., 1987; Smolin et al., 1987] and clinical history. All of the cystinosis subjects had been treated with cysteamine or phosphocysteamine for varying lengths of time. None of the cystinosis subjects was experiencing renal failure at the time of testing and all were euthyroid. All control subjects had normal developmental and medical histories.

Materials and Procedures

All subjects were administered the WRAT-R, according to standardized procedure, as part of a larger study examining the neurocognitive effects of cystinosis. The WRAT-R is comprised of the subtests of arithmetic (counting items, reading of numbers, simple word problems, solving printed arithmetic problems), spelling (copying of symbols, writing of name, writing words to dictation), and reading (letter recognition, letter identification, word pronunciation). The WRAT-R manual provides normative data for ages 5–0 through 74–11 years and standard scores with a mean of 100 and a standard deviation of 15. Standard scores for the three subtests were analyzed using multivariate analysis of variance (MANOVA), with the independent variables of group and sex, and the dependent variables the three subtest scores. Matched pairs *t*-tests were used for follow-up comparisons. In addition, a regression analysis of each subtest score with age was performed to identify any potential relationship between score and age in our cross-sectional study. The data were also examined qualitatively in order to better characterize the cystinosis group's performance.

RESULTS

The arithmetic, spelling, and reading means and standard deviations for the cystinosis and control groups are presented in Table I. MANOVA revealed a significant main effect for Group ($P = .009$). Follow-up comparisons indicated that the cystinosis group performed significantly more poorly ($P = .001$) than did the control group on the arithmetic subtest and that there was a trend ($P = .085$) toward poorer performance by the cystinosis group on the spelling subtest.

TABLE I. Means and Standard Deviations Obtained by the Cystinosis Group and the Control Group on Arithmetic, Spelling, and Reading

Subtest	Cystinosis Group (N = 19)		Control Group (N = 19)		P
	M	SD	M	SD	
Arithmetic	89.95	13.77	102.16	9.62	.001
Spelling	90.68	18.81	98.00	10.96	.085
Reading	97.47	15.59	98.58	12.41	.726

The cystinosis group did not differ significantly from the control group on the reading subtest. The MANOVA revealed no significant main effect for Sex, nor was there a Group x Sex interaction. The cystinosis and control subjects' standard scores on each subtest are plotted in Figure 1. Regression analyses of age with arithmetic, spelling, and reading standard scores revealed no significant correlations in either the cystinosis or control group.

In terms of the *level* of performance on each subtest, the cystinosis group scored at the juncture of the average and low average ranges on both arithmetic (mean = 89.95 ± 13.77) and spelling (mean = 90.68 ± 18.81). They performed within the average range on reading (mean = 97.47 ± 15.59). The control group performed within the average range on each subtest. Given the cystinosis group's generally poorer and more variable performance in comparison to controls (see Table I), the data were also analyzed qualitatively on two dimensions: the first was the number of subjects falling at or below a standard score of 85 (≤16th percentile), indicating an impaired performance. The second was the number of subjects scoring at or above a standard score of 100 (≥50th percentile), indicating an average to

above average performance. Table II presents the number and percentage of cystinosis and control subjects demonstrating "impaired" and "50th percentile+" performance on each of the three subtests. As can be seen in Table II, the number of cystinosis subjects falling in the impaired range is considerably greater than the number of control subjects falling in the impaired range, particularly on the subtests of arithmetic and spelling. Similarly, when considering the number of scores at or above the 50th percentile, there are far fewer cystinosis than control subjects performing at this level.

Since the normative data for the WRAT-R are based on age, whereas academic skills are largely related to grade level in school, it was important to determine whether differences in performance were due to differences in grade level between the two groups. Therefore, a comparison of grade level was performed for all but one of the cystinosis-control pairs (data for one pair were unavailable). Eight cystinosis-control pairs were in the same grade, in six pairs the control was one grade ahead of the cystinosis subject, and in four pairs the cystinosis subject was one grade ahead of the control subject. Moreover, all subjects but two with cystinosis were grade-appropriate for their age. In the case of the two, one cystinosis subject was a year behind and one was a year advanced.

DISCUSSION

The results of this study indicate that, despite normal intelligence and age-appropriate grade level in school, individuals with cystinosis may demonstrate academic difficulties, particularly in arithmetic and to a lesser extent in spelling. The observed difference in academic performance could not be attributed to any difference in educational level between the two groups, since both groups had comparable grade levels. Furthermore, no trends were found between age and standard score for cystinosis subjects on any of the subtests. Hence, in this cross-sectional sample, there was no evidence of either a developmental lag or deterioration of function with age. This might argue for the presence of an early alteration in brain development that produced a static deficit.

The observed academic differences may be related to the underlying visual processing deficits previously identified in these individuals. The visual deficits include difficulty with spatial relationships, part-whole relationships, some aspects of visual memory, mental imagery, and mental rotation. Such difficulties may at least partially explain the arithmetic and spelling performances observed here. Both of these academic skills require multiple aspects of visual processing and visual-spatial integration. Disturbances in these basic cognitive abilities could interfere with normal acquisition of, and proficiency in, certain academic abilities. The observed differences in the cystinosis group do not appear to be simply a problem of delayed learning of academic skills, since the standard scores of the older and younger subjects were similar.

It is possible that the differences in both visual processing and academic skills may reflect a common

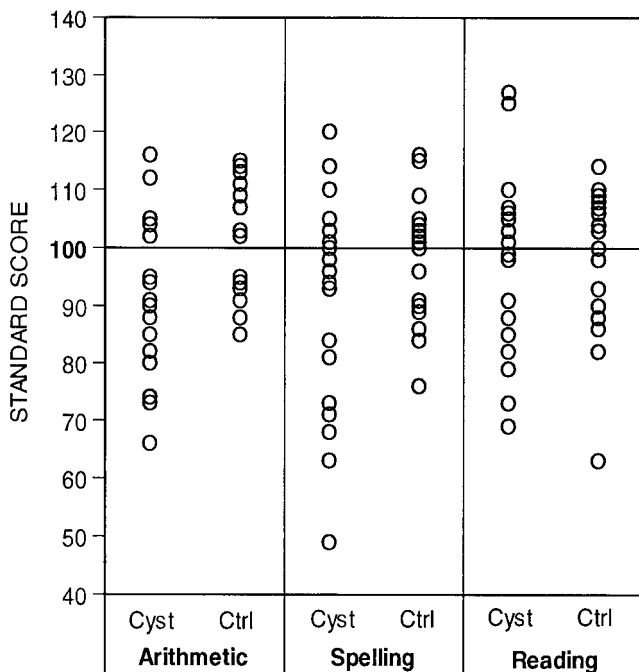


Fig. 1. Standard scores for cystinosis (Cyst) and control (Ctrl) subjects on the Arithmetic, Spelling, and Reading subtests.

TABLE II. Number and Percentage of Cystinosis and Control Subjects Demonstrating "Impaired" and "50th Percentile +" Performance on Arithmetic, Spelling, and Reading

Subtest	Impaired				50th Percentile +			
	Cystinosis		Control		Cystinosis		Control	
	N	%	N	%	N	%	N	%
Arithmetic	8	42	1	5	5	26	12	63
Spelling	7	37	2	11	8	42	11	58
Reading	5	26	2	11	10	53	12	63

mechanism of selective cortical damage by the metabolic disorder. Although a cause for such selective damage has not been identified to date, several hypothetical mechanisms deserve consideration. The genetic defect involves a gene that normally encodes for a transport protein which allows cystine to cross the lysosomal membrane [Gahl et al., 1982a,b]. Cystine is thus trapped within lysosomes. The resultant cystine accumulation within neural tissue may cause functional impairments in cognitive performance in one of two ways: either by a structural alteration in brain development in utero, or by progressive damage as a result of continuing accumulation over time. Other potential mechanisms that might be considered include other, as yet undefined, membrane alterations associated with the genetic defect; or the gene for cystinosis may be contiguous to a gene that influences visual processing or a related cognitive skill.

There is evidence to support a direct effect of cystine accumulation. Cystine has been found to accumulate in the kidneys in utero [Schneider et al., 1974], and it is likely that cystine accumulates in fetal neural tissue as well. This might well produce a static functional deficit such as we observed in this study. There may be progressive cystine accumulation in the brain throughout childhood as well. However, if ongoing cystine accumulation were responsible for differences in cognitive function, individuals with cystinosis might be expected to have progressively poorer performance over time. The present study did not demonstrate such changes with age, but the cross-sectional nature of the study may have obscured a trend toward longitudinal decline. There is as yet no experimental evidence to substantiate the validity of the other two hypothetical mechanisms mentioned above.

There are several caveats that must be taken into consideration in the interpretation of these findings. We cannot completely rule out the possibility that indirect effects of the illness, such as poor school attendance, chronic malaise, medication effects, or other medical factors, could have contributed to poorer performance. Parental reports were obtained on all of the subjects. Most of the children in this study did not have an unusually large number of absences from school compared with controls. Furthermore, there was no indication from parental reports of chronic fatigue or other obvious medical or psychosocial causes of differential academic performance. At this time we are unable to determine whether the various treatments for the underlying disease have any effect on academic performance.

The implications of this research extend beyond the

group of individuals with cystinosis. Carriers of the gene also have elevated cystine levels [Adamson et al., 1989; Gahl, 1986; Gahl et al., 1982a] and may be at risk for subtle cognitive differences. Preliminary studies of carriers demonstrate subtle cognitive [Trauner et al., 1995] and neurophysiologic [Sarfaty et al., 1992] differences compared with controls. Further studies are required to address this issue.

At the present time, there is little information regarding differential localization of cystine in the brain, nor are detailed neuro-anatomic studies available to help define structural features that might correlate with functional differences. Further studies of structure-function relationships may help to elucidate the underlying mechanisms by which cognitive changes occur in this genetic metabolic disorder.

ACKNOWLEDGMENTS

This research was funded by a grant from the National Institutes of Health (RO1 HD 23854) and by a General Clinical Research Center Grant (MO1 RR 00827). We thank Dr. Jerry Schneider for referring the patients for the study. We are grateful to all of the individuals who participated in the study.

REFERENCES

- Adamson MD, Andersson HC, Gahl WA (1989): Cystinosis. *Semin Nephrol* 9:147-161.
- Ebbesen F, Mygind KI, Holck F (1976): Infantile nephropathic cystinosis in Denmark. *Dan Med Bull* 23:216-222.
- Ehrich JHH, Wolff G, Stoeppeler L, Heyer R, Offner G, Brodehl J (1979): Psychosocial intellectual development of children with infantile cystinosis and cerebral atrophy. *Klin Padiat* 191:483-492.
- Gahl WA (1986): Cystinosis coming of age. *Adv Pediatr* 33:95-126.
- Gahl WA, Bashan N, Tietze F, Bernardini I, Schulman JD (1982a): Cystine transport is defective in isolated leukocyte lysosomes from patients with cystinosis. *Science* 217:1263-1265.
- Gahl WA, Tietze F, Bashan N, Steiner R, Schulman JD (1982b): Defective cystine exodus from isolated lysosome-rich fractions of cystinotic leukocytes. *J Biol Chem* 257:9570-9575.
- Jastak S, Wilkinson GS (1984): "Wide Range Achievement Test-Revised." Wilmington, Delaware: Jastak Associates.
- Jonas AJ, Conley SB, Marshall R, Johnson RA, Marks M, Rosenberg H (1987): Nephropathic cystinosis with central nervous system involvement. *Am J Med* 83:966-970.
- Levine S, Paparo G (1982): Brain lesions in a case of cystinosis. *Acta Neuropathol (Berl)* 57:217-220.
- Nichols SL, Press GA, Schneider JA, Trauner DA (1990): Cortical atrophy and cognitive performance in infantile nephropathic cystinosis. *Pediatr Neurol* 6:379-381.
- Sarfaty TD, Coffey SA, Weber-Fox CM, Hodge BL, Trauner DA, Neville HJ (1992): A neurophysiological analysis of visuospatial attention in children with cystinosis, carrier siblings, and controls. *Neurol* 42:278.
- Schneider JA, Verroust FM, Kroll WA, Garvin AJ, Horger EO III, Wong

- VG, Spear GS, Jacobson C, Pellett OL, Becker FLA (1974): Prenatal diagnosis of cystinosis. *N Engl J Med* 290:878–882.
- Smith M, Furlong CE, Green AA, Schneider JA (1987): Cystine: Binding protein assay. *Methods Enzymol* 143:144–148.
- Smolin LA, Clark KF, Schneider JA (1987): An improved method for heterozygote detection of cystinosis, using polymorphonuclear leukocytes. *Am J Hum Genet* 41:266–275.
- Trauner DA, Chase C, Scheller J, Katz B, Schneider JA (1988): Neurologic and cognitive deficits in children with cystinosis. *J Pediatr* 112:912–914.
- Trauner DA, Chase C, Ballantyne A, Tallal P, Schneider J (1989): Patterns of visual memory dysfunction in children with cystinosis. *Ann Neurol* 26:436.
- Trauner DA, Williams BL, Ballantyne AO, Scarvie KM, Schneider J, Chase C (1995): Cognitive deficits in heterozygous carriers of the cystinosis gene. *Pediatr Res* 37:154A.
- Vogel DG, Malekzadeh MH, Cornford ME, Schneider JA, Shields WD, Vinters HV (1990): Central nervous system involvement in nephropathic cystinosis. *J Neuropathol Exp Neurol* 49:591–599.
- Williams BLH, Schneider JA, Trauner DA (1994): Global intellectual deficits in cystinosis. *Am J Med Genet* 49:83–87.
- Wolff G, Ehrich JH, Offner G, Brodehl J (1982): Psychosocial and intellectual development in twelve patients with infantile nephropathic cystinosis. *Acta Paediatr Scand* 71:1007–1011.
- Wolff G, Ehrich JHH, Offner G, Brodehl J (1989): Cognitive and scholastic functioning in patients with infantile nephropathic cystinosis. VIII Congress of the International Pediatric Nephrology Association. Abstract 8.007.