Global Intellectual Deficits in Cystinosis

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Fourteen families of children with infantile nephropathic cystinosis were evaluated using the Stanford-Binet Intelligence Scale, Fourth Edition [Thorndike et al., 1986: Stanford-Binet Intelligence Scale, Fourth Ed.]. The IQs of 15 children with cystinosis, their 23 sibs and 24 parents were compared in order to evaluate a potential effect of cystinosis on intelligence. Children with cystinosis had a significantly lower mean IQ than their sibs and their parents ($P = .001$). Thus, even though the mean IQ of the children with cystinosis (94.4 ± 10) was within the average range, there is evidence that these children have a mild global intellectual deficit relative to their expected IQ based upon the IQs of other relatives. In addition, to a subset of the subjects we administered a measure of scholastic ability, the Wide Range Achievement Test-Revised [Jastak and Wilkinson, 1984: The Wide Range Achievement Test-Revised], which consists of spelling, reading, and arithmetic subtests. The 11 cystinosis subjects scored significantly lower ($P = .01$) than their 16 sibs and their 14 parents in the area of spelling, whereas they did not significantly differ in their performance in the areas of reading and arithmetic.
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INTRODUCTION

Infantile nephropathic cystinosis is an autosomal recessive disorder characterized by lysosomal accumulation and crystalline deposition of cystine in tissues including kidney, thyroid, cornea, and brain. The cystine deposits are known to cause progressive renal and thyroid dysfunction. Cystinosis was originally thought to spare the central nervous system; however, recent investigations have demonstrated cystine accumulation in the brain [Vogel et al., 1990; Jonas et al., 1987; Levine and Paparo, 1982; Ross et al., 1982]. This accumulation may account for the specific cognitive deficit observed in these subjects [Trauner et al., 1988, 1989; Nichols et al., 1990a,b]. These studies have demonstrated an impairment in visual information processing in the presence of normal IQ.

Since there is a strong positive relationship between level of intelligence and degree of kinship [Tyler, 1965; Anastasi, 1958] one would predict that the IQs of children with cystinosis, their sibs, and their parents would be similar if global intelligence remains unaffected in cystinosis. However, if the cystine accumulation in the brain does have an effect on global intellectual functioning, one would expect children with cystinosis to perform differently from other relatives on measures of IQ. The purpose of this study was to examine the IQs of children with cystinosis, their sibs, and their parents in order to determine whether the children with cystinosis performed as well on a measure of global intelligence as one might predict based on the performance of other family members.

METHODS

Sixty-two subjects from 14 families participated in this study, 15 with infantile nephropathic cystinosis, 19 sibs and 4 half-sibs (henceforth together referred to as "sibs"), and 24 parents. Sixteen of the 23 sibs were heterozygous carriers of the cystinosis gene as were all of the 24 parents. The children with cystinosis ranged in age from 2.9 to 19.3 years, the siblings from 2.6 to 34.1 years, and the parents from 26.2 to 62.3 years. Nine of the children with cystinosis were female, and 6 were male. Sixteen of the sibs were female, and 7 were male. Thirteen of the parents were female, and 11 were male.

An abbreviated version of the Stanford-Binet Intelligence Scale, Fourth Edition [Thorndike et al., 1986] was administered to each of these subjects as part of a larger study. The abbreviated version consisted of Vocabulary, Pattern Analysis, Quantitative Analysis, Bead Memory, and Memory for Sentences subtests. These were used to compute area scores representing the four subdivisions of the test (Verbal Reasoning, Abstract/Visual Reasoning, Quantitative Reasoning, and Short-Term Memory), which in turn were compiled to form the composite IQ. The Stanford-Binet is normed from age 2 to 23 years. The composite IQ for all subjects

older than this was estimated using norms for 18- through 23-year-olds.

Background information on general health and school performance was collected on a subset of the subjects. The Wide Range Achievement Test-Revised (WRAT-R) [Jastak and Wilkinson, 1984] was also administered to a subset of our subjects as a measure of their school performance in the areas of reading, spelling and arithmetic. This subset included 11 of the cystinosis subjects, 16 of the sibs, and 14 of the parents in our study. Informed consent was obtained prior to testing each subject in accordance with the Investigational Review Board at the University of California, San Diego.

The relationship of subject IQ with subject group, sex, age, and sib heterozygous carrier status was analysed by one factor analysis of variance (ANOVA) using IQs compiled with and without the Bead Memory subtest. The Bead Memory subtest was excluded in some of the analyses of IQ because it has been shown to be sensitive to the visual spatial deficits of cystinosis subjects [Trauner et al., 1988, 1989] and as such was a possible confounding variable to the calculation of IQ in these subjects. The relationship of subject IQ with age was analysed using a simple regression analysis. In addition, the relationship between subject group and subject WRAT-R performance was analysed by one factor ANOVA for each of the 3 subtests.

Two of the 15 cystinosis subjects had received renal transplants several years prior to testing. Of the remaining 13 subjects with cystinosis, 4 were taking cysteamine at the time of testing, and 9 were taking phosphocysteamine. Four of the subjects were taking a low dose regimen (1.3 $g/m^2/day$) of medication, and 9 were taking a high dose regimen (1.95 $g/m^2/day$). Analyses were run to determine whether treatment type, dose, duration, or age at onset of treatment were a determinant of IQ.

To determine the level of renal functioning, 13 of the 15 cystinosis subjects had creatinine clearance measured near the time (within a mean = 1.9 ± 1.6 months) of psychometric testing. Creatinine clearance (mL/min/1.73 m^2) was defined using the following formula: height (cm) × 0.55/serum creatinine (mg/dL) [Schwartz et al., 1976]. Regression analyses were run to determine if IQ was correlated with creatinine clearance (see Fig. 1).

The thyroid function of the subjects with cystinosis in our study was carefully monitored with T4 and TSH determinations.

None of the children were on carnitine treatment at the time of the study.

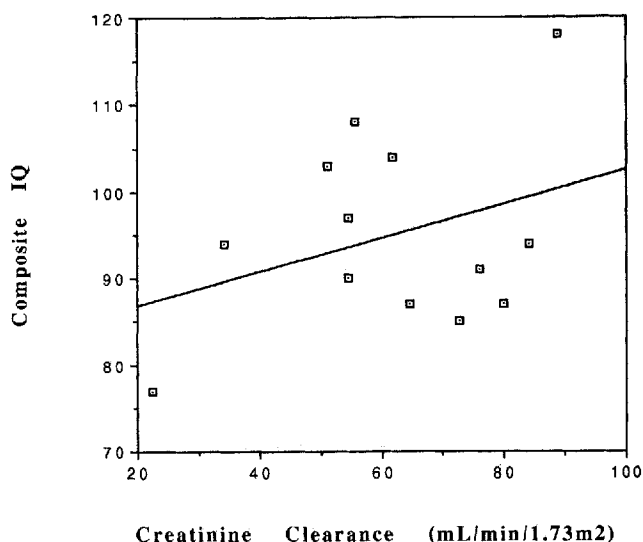$$y = 83.015 + 0.19446x \quad R = 0.341$$

Fig. 1. Relationship between IQ and creatinine clearance in 13 subjects with nephropathic cystinosis. Although there is a trend toward higher IQ with higher creatinine clearance, this relationship is not significant.

RESULTS

The mean composite IQ scores of the children with cystinosis, their sibs, and their parents are summarized in Table I. These mean IQs all lie within the normal range of the Stanford-Binet. The mean IQ scores of heterozygous sibs and nonheterozygous sibs did not differ significantly and were 108.2 ± 11 and 107.1 ± 2.5, respectively. Therefore for these analyses they were considered as one group.

All analyses were run using the IQ score compiled including the Bead Memory subtest and the IQ score compiled excluding the Bead Memory subtest. The results of analyses of IQ with Bead Memory and those without Bead Memory were entirely consistent with one another.

ANOVA showed that the 3 groups differed significantly on mean composite IQ ($P = .001$), and planned comparisons were significant at 95% for comparisons of children with cystinosis to both their sibs and parents. There were no significant differences in IQ between males and females in any of the 3 groups. Age did not

TABLE I. Mean Stanford-Binet IQs (4th Edition)

	Total no.	No. female	No. male	Age (years)	IQ w/BM[a]	IQ w/o BM
Children with cystinosis	15	9	6	7.8 ± 4.3	94.4 ± 10	96.4 ± 11
All siblings	23	16	7	12.85 ± 7.4	107.7 ± 9.0	107.4 ± 8.6
Carrier siblings	16	10	6	12.27 ± 7.5	108.2 ± 11	107.8 ± 10
Noncarrier siblings	7	6	1	14.17 ± 6.7	107.1 ± 2.5	106.6 ± 3.2
Parents	24	13	11	38.38 ± 8.7	103.8 ± 12	105.2 ± 12.4[b]

[a] BM, Bead Memory.
[b] n = 23, unable to calculate the IQ without Bead Memory of one of the female subjects.

TABLE II. Mean Wide Range Achievement Test: Revised Results

	Total no. of subjects	Reading standard score	Spelling standard score	Arithmetic standard score
Cystinosis subjects	11	91.4 ± 16	84.3 ± 19	89.5 ± 15
Siblings	16	103 ± 9.0	100 ± 16	98.5 ± 13
Parents	14	103 ± 9.0	103 ± 12	95.7 ± 11

significantly correlate with IQ for the sibs or the children with cystinosis.

The mean scores for the WRAT-R in the areas of reading, arithmetic and spelling are found in Table II. The three groups did not significantly differ in performance on the reading and arithmetic subtests of the WRAT-R. A one-way ANOVA revealed that group and WRAT-R spelling performance did significantly differ (P = .01) and planned comparisons showed that the children with cystinosis (Spelling Standard Score = 84.3 ± 19) scored significantly lower than their parents (SS = 103 ± 12) and sibs (SS = 100 ± 16).

The IQs of the 2 subjects evaluated postrenal transplant were 97 and 87; the mean of the remaining 13 subjects was 95.0 ± 11. When analyses were run without the transplanted subjects, ANOVA showed that the groups still significantly differed on IQ (P = .009), but the planned comparison showed that the cystinosis subjects significantly differed from the sibs and not the parents.

There were no significant differences found between the IQs of subjects who were medicated with cysteamine compared to those taking the alternative variant of the drug, phosphocysteamine. There was also no significant difference between subjects who were taking "high" versus "low" doses of the 2 drugs. Neither the duration of medical treatment nor age at onset of treatment correlated with IQ (Table III).

Two of the 15 subjects had creatinine clearance levels that were below the normal to mildly abnormal range (<50 mL/min/1.73 m^2). IQ was found not to be significantly correlated with creatinine clearance levels through regression analysis (R = .341).

Four of the subjects were being treated for hypothyroidism at the time of testing. Their mean IQ was 95.5 ± 6 which did not differ significantly from the IQ of the remaining 11 subjects (mean IQ = 94.0 ± 11).

DISCUSSION

Previous studies [Wolff et al., 1982, 1989] have shown IQ to be within the normal range in subjects with cystinosis, and based on these findings they have concluded that there was no negative effect on IQ in cystinosis.

However, these studies did not compare cystinosis subjects with their sibs or parents. Results of our present study indicate that despite having IQs within the normal range, children with infantile nephropathic cystinosis may have a previously undetected global intellectual impairment. This conclusion is based on the significantly lower mean IQ of cystinosis subjects when compared to that which would be predicted based on the IQs of their sibs and parents. This result indicates a possible neurotoxic effect of progressive cystine accumulation in the brain. Other possible causes for their poorer performance include chronic renal failure, renal transplantation, acquired hypothyroidism, side effects of their treatment medication, and/or psychosocial factors related to chronic illness.

Previous studies have shown that children with cystinosis have a specific cognitive impairment in the processing of visual information. These deficits were not seen in subjects with chronic renal dysfunction from other causes [Trauner et al., 1988, 1989]. Therefore, these studies indicate that the visual spatial impairment in children with cystinosis seems to be related to the underlying metabolic disorder rather than to the effects of their renal dysfunction. The findings of the present study may also relate to the underlying metabolic disorder. It is possible that impaired renal function could contribute to the relative IQ depression seen in our cystinosis subjects. To examine this possibility, we determined creatinine clearance, as a measure of renal function, on 13 of the 15 subjects near the time of their IQ evaluation. IQ was not significantly correlated with the creatinine clearance. Only 2 of the 15 subjects had creatinine clearance levels that were below the normal to mildly abnormal range (<50 mL/min/1.73 m^2). Since the majority of the cystinosis subjects had renal function within normal to mildly abnormal limits near the time of testing, and since the level of creatinine clearance did not significantly correlate with IQ performance, it is unlikely that renal impairment contributed substantially to the IQ depression of these subjects.

Two of the 15 cystinosis subjects in the study had received kidney transplants several years prior to our testing. It is difficult to assess whether their renal fail-

TABLE III. Cysteamine Usage Data

	Low dose/ phosphocysteamine (mean ± S.D.)	High dose/ phosphocysteamine (mean ± S.D.)	Low dose/ cysteamine (mean ± S.D.)	High dose/ cysteamine (mean)
Number of subjects	6	3	3	1
Mean IQ	95.3 ± 11	93.3 ± 6.9	93.0 ± 13	104
Mean treatment duration (in years)	2.85 ± 1.4	3.95 ± 1.0	6.28 ± .10	6.67
Mean treatment starting age (in years)	1.67 ± .90	3.89 ± .79	2.42 ± .99	2.42

ure earlier in life had an impact on their IQ. The composite IQ scores of these 2 patients were 87 and 97 which are within the range of the cystinosis subjects without transplants (mean IQ: 95.0 ± 11). We cannot rule out altogether the possibility that chronic renal problems and renal transplantation contribute to lower IQ. However, since the 2 transplanted subjects had IQ levels comparable to those of the subjects without transplants, transplant status makes no obvious contribution to the IQ depression found in the present study.

Acquired hypothyroidism is a potential complication of infantile nephropathic cystinosis, due to the extensive accumulation of cystine in the thyroid glands of these subjects. The thyroid function of the subjects with cystinosis in our study was carefully monitored with T4 and TSH determinations. The children received treatment as soon as TSH levels became elevated, prior to development of clinical hypothyroidism. Since treatment is prompt, it is unlikely that thyroid dysfunction plays a significant role in the IQ depression seen in the subjects in our study. Depression of IQ is a recognized complication of untreated congenital hypothyroidism [Murphy et al., 1990]. It is thought that hypothyroidism has its greatest effect on human cognitive functioning in the first several months of life [Rovet et al., 1984]. The subjects in our study undergoing treatment for hypothyroidism all developed elevated TSH levels after age 2 years and were treated within 3 months of the increase. Only 4 of our subjects with cystinosis were on thyroid replacement medication at the time of testing. Their mean IQ was 95.5 ± 6 which did not differ significantly from the IQ of the remaining 11 subjects (mean IQ = 94.0 ± 11).

Another possible factor contributing to the IQ differences of the children with cystinosis is the effect of cysteamine and phosphocysteamine on the brain. It is unknown whether these medications can penetrate the blood brain barrier in humans. Thus, the effect of these drugs on brain levels of lysosomal cystine accumulation is unknown. In our study, there are very few cystinosis children who have never received cysteamine treatment. Therefore, comparisons cannot be made between those subjects that have received treatment and those that have not. Consequently, there is not enough information to know if cysteamine has any effect, either positive or negative, on IQ. To examine the effects of cysteamine and phosphocysteamine treatment on IQ, comparisons were made between subjects based on treatment duration and age at onset of treatment. Thirteen of the 15 children with cystinosis were participants in a study of cysteamine or phosphocysteamine treatment. The duration of the treatment and the age of treatment onset did not correlate with IQ. Thus, we have no evidence that the cysteamine treatment status of the cystinosis subjects in this study contributed to their IQ scores.

Potential psychosocial factors that might have contributed to the observed difference in I.Q. include feeling poorly because of the underlying illness, poor school attendance, and the adverse impact of short stature and the appearance of being younger than their chronological age. Once these children were diagnosed with their metabolic disorder, their medical problems were well-controlled. There was no evidence, by parental report, that the children were chronically fatigued or felt poorly most of the time. With reference to the short stature and youthful appearance, we have no means of assessing the potential negative impact on I.Q. of these conditions. We are in the process of conducting studies of behavior, personality, and social skills in children with cystinosis. Such studies may provide more information regarding the effects of psychosocial difficulties on cognitive function or performance.

We do have information regarding school attendance. One of the complications of a chronic illness is missing more school than the average child. This in turn may contribute to poorer performance on standardized tests. Information on school attendance was obtained on 13 of the 15 children with cystinosis and on 15 of the 23 sibs. In general, the children with cystinosis and their sibs tended to receive public schooling, performed within the average to above average range in school as did their sibs, and missed about the same amount of school as their sibs. One child with cystinosis received home schooling as did his sib. Only one child with cystinosis received any special education, whereas 2 sibs received special education and one sib was in speech therapy. Since the children with cystinosis in this group of subjects are so similar to their sibs in terms of school attendance and performance, it is unlikely that the psychosocial effects of chronic illness and school absence are related to the significantly lower IQ relative to their sibs noted in this study.

In addition, to further examine school performance, a subset of 11 cystinosis subjects in this study was compared to their 16 sibs and 14 parents on the WRAT-R. The cystinosis subjects did not perform significantly differently from their sibs and parents on measures of reading and arithmetic. However, they did perform significantly less well than their sibs and parents on the spelling subtest. Further studies are required to determine the significance of a potential isolated problem with spelling in this group.

The lower global IQ scores found in this study do not appear to be a direct function of the problems with visual processing noted in children with cystinosis. To address this possibility, analyses were run excluding the Bead Memory subtest from the IQ tabulation. This task evaluates short-term visual memory, and Trauner et al. [1988] previously reported that subjects with cystinosis perform more poorly on this test than do unrelated controls. Even with the Bead Memory subtest excluded from the analyses, the significant differences in IQ remained. Thus, it is likely that their lower IQ scores are not due solely to their visual processing deficit, but rather to a more global intellectual impairment.

Finally, it is possible that the cognitive changes we are observing are not due to the cystinosis, but rather to a closely linked gene that is also affected. This is an intriguing possibility that is being explored further.

Now that children with cystinosis are surviving into adulthood, the effects of progressive cystine accumulation on the brain need to be examined. Further study is needed to clarify the origin of these cognitive deficits as

well as to assess the potential effects of various treatment modalities.

REFERENCES

Anastasi A (1958): "Differential Psychology" (3rd edition). New York, NY: The Macmillan Company, pp 266–316.

Jastak S, Wilkinson GS (1984): The Wide Range Achievement Test-Revised. Wilmington, Delaware: Jastak Associates, Inc.

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.

Murphy GH, Hulse JA, Smith I, Grant DB (1990): Congenital Hypothyroidism: Physiological and Psychological Factors in Early Development. J Child Psychol Psychiat 31:711–725.

Nichols SN, Ballantyne AO, Hodge BL, Trauner DA (1990a): Further characterization of the visual processing deficit in nephropathic cystinosis. Society for Neuroscience Abstracts 16:1240.

Nichols SL, Press GA, Schneider JA, Trauner DA (1990b): Cortical atrophy and cognitive performance in Infantile Nephropathic Cystinosis. Pediatr Neurol 6:379–381.

Ross DL, Strife CF, Towbin R, Bove KE (1982): Nonabsorptive hydrocephalus associated with nephropathic cystinosis. Neurol 32:1330–1334.

Rovet JF, Westbrook D, Ehrlich RM (1984): Neonatal Thyroid Deficiency: Early Temperamental and Cognitive Characteristics. J of the Am Academy of Child Psychiat 23:10–22.

Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A (1976): A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatr 58:259–263.

Thorndike R, Hagen E, Sattler J (1986): Stanford-Binet Intelligence Scale, Fourth Ed. Chicago, Illinois: Riverside Publishing.

Trauner DA, Chase C, Ballantyne A, Tallal P, Schneider J (1989): Patterns of visual memory dysfunction in children with cystinosis. Ann of Neurol 26:436.

Trauner DA, Chase C, Scheller J, Katz B, Schneider J (1988): Neurologic and cognitive deficits in children with cystinosis. J of Pediatr 112:912–914.

Tyler LE (1965): "The Psychology of Human Differences" (3rd edition). New York, NY: Appleton-Century-Crofts, pp 475–499.

Vogel DG, Malekzadeh MH, Cornford ME, Schneider JA, Shields WD, Vinters HV (1990): Central nervous system involvement in nephropathic cystinosis. J Neuropathol and Experimental Neurol 49:591–599.

Wolff G, Ehrich JH, Offner G, Bodehl J (1989): Cognitive and scholastic functioning in patients with Infantile Nephropathic Cystinosis. VIIth Congress of the International Ped Nephrol Assn, Toronto, #8.007.

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.