

VISUOMOTOR PERFORMANCE IN CHILDREN WITH INFANTILE NEPHROPATHIC CYSTINOSIS^{1, 2}

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Summary.—Infantile nephropathic cystinosis is a genetic metabolic disorder in which the amino acid cystine accumulates in various organs, including the kidney, cornea, thyroid, and brain. Despite normal intellect, individuals with cystinosis may have specific impairments in the processing of visual information. To examine further the specific types of deficits in visual processing found in individuals with cystinosis, we administered the Developmental Test of Visual-motor Integration to 26 children with cystinosis (4 to 16 yr. old) and 26 matched controls. The cystinosis group achieved a significantly lower standard score, raw score, and mean ceiling than did the control group. Qualitative analyses showed that in the cystinosis group, size within errors and rotation errors were more prevalent than in the control group. Correlational analyses showed that with advancing age, the cystinosis subjects tended to fall further behind their chronological age. Our data, together with the findings of previous studies, suggest that the visuospatial difficulties in children with cystinosis may be due to inadequate perception or processing of visually presented information. Furthermore, the increasing discrepancy with age may reflect a progressive cognitive impairment, possibly as a result of cystine accumulation in the brain over time.

Infantile nephropathic cystinosis is an autosomal recessive metabolic disorder in which the amino acid cystine accumulates in the lysosomes. Manifestations of the disease include deposition of cystine crystals in various organs (e.g., kidney, cornea, thyroid, brain), growth failure, renal failure, and hypothyroidism. Neurologic deficits identified in cystinosis include impaired gross and fine motor skills, hypotonia, and tremor (Trauner, Chase, Scheller, Katz, & Schneider, 1988).

Prior research has indicated that as a group, individuals with cystinosis have over-all intelligence that is within the normal range (Fink, Brouwers, Barton, Malekzadeh, Sato, Hill, Cohen, Fivush, & Gahl, 1989; Trauner, *et*

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al., 1988; Williams, Schneider, & Trauner, 1994; Wolff, Ehrich, Offner, & Brodehl, 1982). Despite normal intellect, however, individuals with cystinosis have specific impairments in the processing of visual information. Individuals with cystinosis have difficulty on a complex, short-term visual-memory task (Trauner, *et al.*, 1988). Increasing exposure time on this task resulted in improved performance. It has also been noted that children with cystinosis are impaired in maintaining in memory internal details of a figure, whereas they are as likely as controls to recall accurately the over-all Gestalt of a figure (Nichols, Ballantyne, Hodge, & Trauner, 1990).

A study of event-related brain potentials (ERPs) in children with cystinosis indicated impairments of selective visual attention (Sarfaty, Coffey, Weber-Fox, Hodge, Trauner, & Neville, 1992). In studies using brain-imaging techniques [magnetic resonance imaging (MRI) or computed tomography (CT)], children with cystinosis showed evidence of both cortical (Fink, *et al.*, 1989; Nichols, Press, Schneider, & Trauner, 1990; Wolff, *et al.*, 1982) and subcortical abnormalities (Hodge, Hesselink, & Trauner, 1992). The latter authors suggested that these abnormalities may be related to some of the specific cognitive deficits found in individuals with cystinosis. At the present time, the long-term effects of ongoing cystine accumulation on cognitive functioning are not known.

In the present study, we administered the Developmental Test of Visual-motor Integration (Beery & Buktenica, 1989) to children with cystinosis and matched controls in order to better characterize the visual processing abnormalities previously noted. Not only were the two groups compared on over-all performance, but also a detailed analysis of error types was performed. This test requires the copying of increasingly complex figures, and unlike the tasks used in some of the previous reports, it does not involve a memory component. Given the results of prior studies, e.g., visual memory deficits, difficulty with spatial relations, we hypothesized that children with cystinosis would perform more poorly on this task than would matched controls. In addition, we applied a qualitative error analysis to assess whether there were differential error-types made by the individuals with cystinosis and their matched controls. Furthermore, we wanted to examine age effects in this cross-sectional group to clarify whether children with cystinosis exhibited declining performance with age, which could be associated with the accumulation of cystine over time.

METHOD

Twenty-six children with infantile nephropathic cystinosis and 26 control subjects were administered the Developmental Test of Visual-motor Integration according to standardized procedures (Beery, 1989). Children with cystinosis and control subjects were individually matched on the basis of age

(± 1 year) and sex. The cystinosis group ranged in age from 4.4 to 16.7 years ($M=8.7$); the controls ranged in age from 4.8 to 15.8 years ($M=8.7$). Each group contained 14 boys and 12 girls. None of the children in the cystinosis group were experiencing renal failure at the time of testing, all were euthyroid, and all were free of uncorrected visual difficulties. The cystinosis group obtained a mean Composite IQ well within the average range (Stanford-Binet Intelligence Scale-Fourth Edition; $M=98.3$, $SD=12.3$; $n=23$). The control subjects had normal developmental histories and were free of motor and uncorrected visual difficulties. Informed consent was obtained prior to testing each subject in accordance with the Institutional Review Board at the University of California, San Diego.

The tests were administered and scored according to the procedure outlined in the test manual. The following scores were calculated: raw score, standard score ($M=100$, $SD=15$), age equivalent, number of items completed (ceiling), and number of items failed. An "age difference" score was computed by subtracting the chronological age from the age equivalent. As indicated in the manual, each test item is subject to multiple scoring criteria; each criterion violated constitutes an "error." We analyzed the number of errors committed over-all as well as the ratio of the number of errors per item failed. The standard scores were analyzed using a paired t test; all other data were analyzed using the Wilcoxon signed-ranks test.

Correlations were calculated to examine the associations of age and the measures of raw score, age equivalent, "age difference" score, number of items completed (ceiling), number of items failed, and ratio of number of errors per item failed.

For each scoring criterion not met, i.e., error, a qualitative error type was assigned. The qualitative error definitions were devised in our laboratory [see Appendix (p. 75) for descriptions of error types]. Qualitative error types included (a) misplacement: gap/overlap, (b) misplacement: directional, (c) shape distortion, (d) shape substitution, (e) size within, (f) size between, (g) addition, (h) omission, (i) rotation, and (j) angle. The probability of each error type being assigned is unequal; therefore, we were not able to make comparisons between error types, only between the cystinosis group and control group on each type of error. (For a detailed description of the qualitative scoring system, please contact the authors.) Qualitative error types were analyzed using the Wilcoxon signed-ranks procedure.

The scoring of the tests and the assessment of qualitative error types were done without reference to group membership. All scoring was done by two independent scorers, with any discrepancies settled by consensus with a third scorer.

RESULTS AND DISCUSSION

Over-all Performance

The means and standard deviations obtained by the cystinosis group and the control group for measures of over-all performance are summarized in Table 1. The cystinosis group achieved a significantly lower standard score than did the control group; the cystinosis group mean was below average, whereas the control mean was average. The raw score was also significantly lower for the cystinosis group. Further analysis indicated that the cystinosis group had a significantly lower mean ceiling than did the controls. Interestingly, the cystinosis group did not fail significantly more items than controls, and they did not fail a significantly greater number of scoring criteria than did controls. As expected, a ratio of number of errors per item failed showed no significant differences. Rather, the cystinosis group's significantly lower standard score and raw score appears attributable to its lower ceiling.

TABLE 1
MEANS AND STANDARD DEVIATIONS OBTAINED BY THE CYSTINOSIS GROUP AND
THE CONTROL GROUP FOR MEASURES OF OVER-ALL PERFORMANCE

Measure	Cystinosis Group		Control Group		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Standard Score	88.6	11.5	100.3	9.8	<.01
Raw Score	15.5	7.1	22.4	11.7	.04
Ceiling	16.4	4.3	18.7	4.7	.01
Number Failed	4.4	1.3	4.0	1.4	.24
Number Scoring Criteria Failed	6.2	2.2	5.2	2.2	.11
Number Errors/Item Failed	1.4	.3	1.3	.3	.23

Analyses of Qualitative Error

Of the ten qualitative error types possible, there was a tendency for the cystinosis group to make more size within ($p = .04$) and rotation ($p = .05$) errors than did controls. Examples of size within and rotation error types are shown in Fig. 1. Error scores for all other error types did not differ significantly between the two groups.

Correlations With Age

In the cystinosis group, the number of items failed increased with age ($r^2 = .15$, $p = .05$). In the control group, the number of items failed did not significantly correlate with age ($r^2 = .09$, $p = .14$). In both the cystinosis and control groups, raw score significantly increased with age (cystinosis: $r^2 = .60$, $p < .01$; control: $r^2 = .89$, $p < .01$). In addition, age and age-equivalent performance showed a significant, positive correlation in both groups (cystinosis: $r^2 = .36$, $p < .01$; control: $r^2 = .80$, $p < .01$). The correlation between age and the age-difference score was significant for the cystinosis group ($r^2 = .51$, $p < .01$),

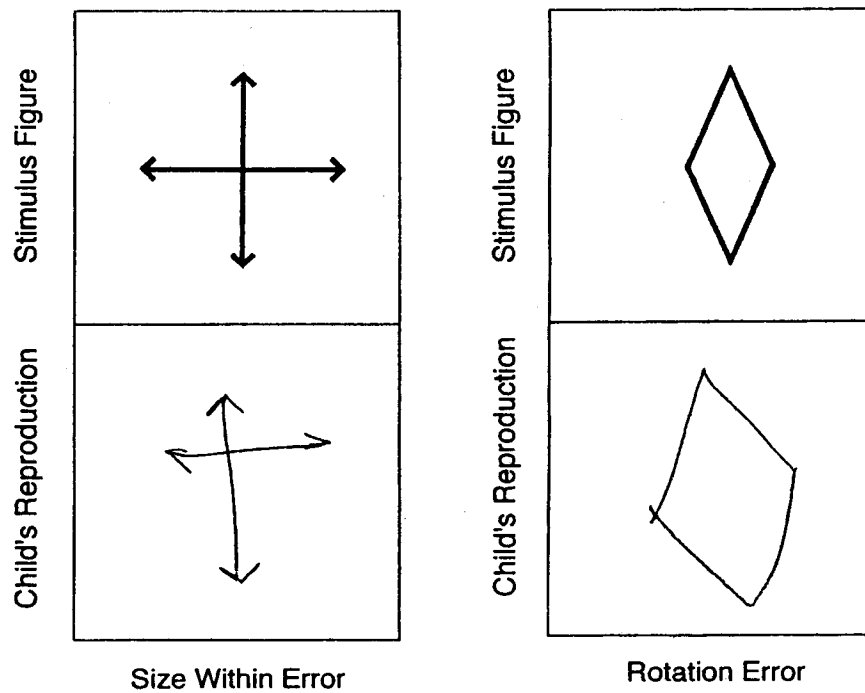


FIG. 1. Examples of size within and rotation qualitative error types. *Note.*—Stimulus figures from Developmental Test of Visual-motor Integration by K. E. Beery and N. A. Buktenica, 1989, Cleveland, OH: Modern Curriculum Press. Copyright 1989 by Keith E. Beery. Reprinted with permission.

indicating that for older children (those in the teen years) the cross-section of subjects in the cystinosis group tended to fall further behind their chronological age (see Fig. 2). In contrast, there was no significant correlation between age and the age-difference score in the control group; they did not perform differently from what was expected for their ages.

On the test of visual-motor integration, children with cystinosis demonstrated significant impairment in comparison to controls. The cystinosis group not only achieved a significantly lower standard score but also had a lower ceiling than did controls. Interestingly, both groups failed approximately the same number of items and violated approximately the same number of scoring criteria. In addition, the cystinosis group and control group were similar in terms of the number of errors per failed item. This suggests that children with cystinosis show subtle, rather than gross, impairments in visuomotor abilities.

Although the present study utilized a cross-sectional design, we analyzed the effect of age on performance in the cystinosis and control groups.

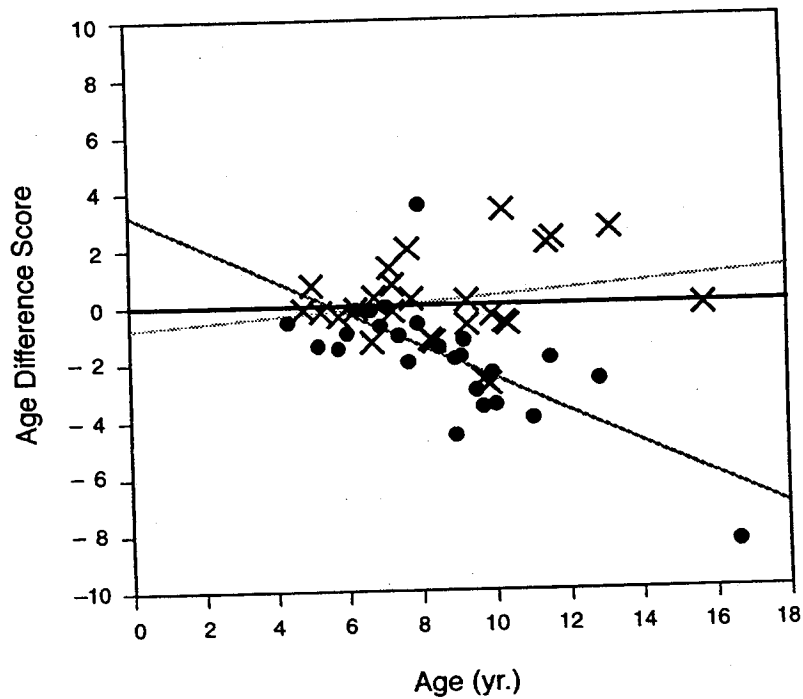


FIG. 2. Scatterplot of age difference score and chronological age for subjects in the cystinosis group (●) and the control group (×). The age difference score represents the difference between the age equivalent score and the chronological age. Bold line at zero represents what would be expected, i.e., no difference between age equivalent score and the chronological age. Regression lines are shown for the cystinosis and control groups.

Such information could help to identify possible underlying causes for the cognitive differences, e.g., if there is merely a developmental delay in acquisition of visual motor skills, then we would expect to see similar evidence of improvement in performance as a function of age for the two groups, but with the cystinosis group lagging slightly behind. If, on the other hand, the detrimental effects of cystine deposition in the nervous system are cumulative, then we might expect to see greater discrepancies in performance between the two groups among the older subjects. In both the cystinosis and control groups, the raw score on this test significantly increased with age. However, correlations indicated that as the ages of individuals in the cystinosis group increased, their visuomotor integration skills fell farther below those appropriate for their chronological ages. Individuals in the control group, on the other hand, performed as expected for their ages. In addition, older children with cystinosis failed more items than younger ones, whereas in the control group, age was not correlated with the number of items failed. These findings suggest that the differences in test performance may not be

merely the result of a maturational lag that parallels normal visuomotor development but rather may reflect the cumulative effects of the metabolic deficit on the brain. There was no obvious difference in the general medical or neurological condition of the older cystinosis subjects compared with the younger subjects; however, it is possible that subtle differences in these conditions could have caused the observed difference in test performance for these small groups.

The controls had more opportunity to make errors because their ceiling was higher, but the error rate between the cystinosis group and controls was similar. Interestingly, our exploration of qualitative error types suggested that size within and rotation errors were *more* likely to occur in the cystinosis group than in the control group. These error types appear consistent with previous research findings indicating that individuals with cystinosis have difficulty with spatial relationships. Similar to earlier findings (e.g., Nichols, Ballantyne, Hodge, & Trauner, 1990), types of errors made by the cystinosis group in this study can be characterized as subtle rather than gross.

The difficulty that individuals with cystinosis exhibit on this test could be related to fine motor deficits previously reported in this disorder (Trauner, *et al.*, 1988). This is not likely, however, given the nature of the types of errors made. Also, visuospatial impairments have been found even on tasks that do not require a motor component (Sarfaty, *et al.*, 1992; Trauner, Chase, Ballantyne, Tallal, & Schneider, 1989). Hence, the visuospatial difficulties observed in the current study are not likely to be simply the result of a motor deficiency.

Previous studies (Nichols, Chase, Ballantyne, Hodge, Tallal, & Trauner, 1991; Nichols, Ballantyne, Hodge, & Trauner, 1990; Nichols, Press, Schneider, & Trauner, 1990; Trauner, *et al.*, 1988, 1989) have documented visual-processing deficits on memory tasks. Since the Developmental Test of Visual-motor Integration does not involve a memory component, the difficulty that individuals with cystinosis experience is unlikely to be attributed to a primary impairment of visual memory. Rather, the deficit observed in cystinosis appears to be one of inadequately perceiving or processing information presented in the visual modality.

The basis for this visual-processing difference is unknown. It may be that accumulation of cystine within the central nervous system selectively affects neuronal populations responsible for processing visual information. The fact that the gap between expected and actual performance increases with age would be compatible with a slowly increasing accumulation of cystine (or other potential neurotoxins) over time or with some other as yet undefined cumulative effect of the metabolic disorder on the central nervous system.

The results documented in the current study expand the existing information regarding the type of visual-processing deficit associated with infantile nephropathic cystinosis. Larger numbers of children for each age category and a broader range of tasks would increase the power of observations. Further studies may help to define the underlying neuroanatomic, neurochemical, and neurobehavioral underpinnings of this deficit.

REFERENCES

- BEERY, K. E. (1989) *Developmental Test of Visual-motor Integration: administration, scoring, and teaching manual*. (3rd rev.) Cleveland, OH: Modern Curriculum Press.
- BEERY, K. E., & BURKENICA, N. A. (1989) *Developmental Test of Visual-motor Integration (long form)*. Cleveland, OH: Modern Curriculum Press.
- FINK, J. K., BROUWERS, P., BARTON, N., MALEKZADEH, M. H., SATO, S., HILL, S., COHEN, W. E., FIVUSH, B., & GAHL, W. A. (1989) Neurologic complications in long-standing nephropathic cystinosis. *Archives of Neurology*, 46, 543-548.
- HODGE, B. L., HESSELINK, J. R., & TRAUNER, D. A. (1992) MRI study of white matter changes in cystinosis. *Society for Neuroscience Abstracts*, 18, 333.
- NICHOLS, S. N., BALLANTYNE, A. O., HODGE, B. L., & TRAUNER, D. A. (1990) Further characterization of the visual processing deficit in nephropathic cystinosis. *Society for Neuroscience Abstracts*, 16, 1240.
- NICHOLS, S. N., CHASE, C., BALLANTYNE, A., HODGE, B., TALLAL, P., & TRAUNER, D. (1991) Complex visual processing time in infantile nephropathic cystinosis. *Annals of Neurology*, 30, 469. [Abstract]
- NICHOLS, S. L., PRESS, G. A., SCHNEIDER, J. A., & TRAUNER, D. A. (1990) Cortical atrophy and cognitive performance in infantile nephropathic cystinosis. *Pediatric Neurology*, 6, 379-381.
- SARFATY, T. D., COFFEY, S. A., WEBER-FOX, C. M., HODGE, B. L., TRAUNER, D. A., & NEVILLE, H. J. (1992) A neurophysiological analysis of visuospatial attention in children with cystinosis, carrier siblings, and controls. *Neurology*, 42, 278. [Abstract]
- TRAUNER, D. A., CHASE, C., BALLANTYNE, A., TALLAL, P., & SCHNEIDER, J. (1989) Patterns of visual memory dysfunction in children with cystinosis. *Annals of Neurology*, 26, 436. [Abstract]
- TRAUNER, D. A., CHASE, C., SCHELLER, J., KATZ, B., & SCHNEIDER, J. A. (1988) Neurologic and cognitive deficits in children with cystinosis. *Journal of Pediatrics*, 112, 912-914.
- WILLIAMS, B. L. H., SCHNEIDER, J. A., & TRAUNER, D. A. (1994) Global intellectual deficits in cystinosis. *American Journal of Medical Genetics*, 49, 83-87.
- WOLFF, G., EHRLICH, H. H., OFFNER, G., & BRODEHL, J. (1982) Psychosocial and intellectual development in 12 patients with infantile nephropathic cystinosis. *Acta Paediatrica Scandinavica*, 71, 1007-1011.

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APPENDIX

TYPES OF ERROR ON VISUAL-MOTOR INTEGRATION

- Misplacement: Gap/Overlap*—Distortion of the spacing between the elements of a multi-element design. The elements either gap or overlap too much.
- Misplacement: Directional*—One element in a multi-element figure is misplaced up, down, left, or right in relation to the other elements in the figure.
- Shape Distortion*—The over-all shape of a figure is distorted. Not a rotation, angle, addition, or omission error, i.e., the figure drawn resembles the figure to be drawn, but is distorted.
- Shape Substitution*—Inaccurate reproduction of a figure by simple substitution, i.e., the figure drawn does not resemble the figure to be drawn.
- Size Within*—In a one-figure design, a portion of a figure is exaggerated or reduced. In one element of a multi-element figure, the relationship between two portions of the element is exaggerated or reduced.
- Size Between*—In a multi-element figure, one of the elements is exaggerated or reduced in comparison to the other element(s) of the figure.
- Addition*—The addition of another element to a figure, or too many of an existing element are reproduced.
- Omission*—The omission of a figure or an element in a figure, or too few of an existing element are reproduced.
- Rotation*—The rotation of a figure, or element in a multi-element figure, in relation to horizontal and/or vertical.
- Angle*—The angle between two lines is exaggerated or reduced.