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Specific Cognitive Deficits in Young Children with Cystinosis:

Evidence for an Early Effect of the Cystinosis Gene on Neural Function

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Abstract

Objectives—Infantile nephropathic cystinosis is associated with a specific cognitive deficit in visual spatial processing in older children and adults. The cause of this deficit is unknown. This study was designed to determine whether the cognitive deficit is present in young children with cystinosis, suggesting an early effect of the genetic disorder on brain development.

Study design Young children (n=25; ages 3– 8 years) with cystinosis, and 25 matched controls, underwent cognitive testing including tests of intelligence, visual perceptual, visual spatial, and visual motor functions.

Results—Children with cystinosis performed significantly more poorly on tests of visual spatial and visual motor function than did controls. Visual perceptual abilities were equivalent in the two groups.

Conclusion—The fact that the same pattern of visual spatial deficit is present in very young children with cystinosis as has previously been demonstrated in older children and adults suggests that there may be an influence of the cystinosis gene on brain development, rather than an adverse effect of prolonged cystine accumulation in the brain during childhood.

Keywords

visual perception; visual spatial; cystinosis

Nephropathic cystinosis is an autosomal recessive disorder of cystine transport. The gene, **CTNS**, mapped to chromosome 17p13 (1-3), codes for a lysosomal membrane transporter protein, cystinosin. When there is an inactivating mutation of the cystinosin gene, cystine cannot be transported across the lysosomal membrane (4). Sequestration and accumulation of cystine within lysosomes occurs as a result.

Infantile nephropathic cystinosis presents within the first year of life with failure to thrive and signs of a generalized defect of renal tubular reabsorption (renal Fanconi syndrome). The natural history of untreated cystinosis is that of progressive renal failure over the first decade of life, with renal transplant required by 10–12 years of age. However, treatment with cysteamine, a cystine-depleting agent, can delay the progression of the renal disease for many years (4).

In untreated individuals with cystinosis, cystine deposition is present in virtually all organs, including the brain (5-6). Generalized cerebral atrophy and central volume loss have been

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documented(7-9). To date the youngest child with cerebral atrophy reported was 7 years old and in renal failure (7). Of most functional significance is the documentation of a specific cognitive impairment in visual spatial processing on a foundation of normal intellectual function (10-12). This deficit is associated with intact visual perception, but impaired spatial processing and memory (10,12), and is associated with deficits in mathematical skills (13). Two studies have found cognitive impairment and more severe cortical atrophy on neuro-imaging studies of school-age children and adults with cystinosis. Both studies were cross-sectional studies, and it is not known whether the anatomic changes preceded or followed the cognitive impairments (15-16).

The cause of the observed cognitive deficit is unknown. Neuropathological reports are scarce, but, because of widespread cystine accumulation (5-7,9,14) in the brains of patients with cystinosis, it is possible that deposition may lead to progressive cellular damage and subsequent impairment in function.

Alternatively, the CTNS gene might influence some aspect of brain development. This could occur as a result of in utero cystine deposition during a critical time in brain development. If cumulative cystine deposition during childhood is responsible for the cognitive differences observed in subjects with cystinosis, it might be expected that young children, especially those treated early with cysteamine, would not demonstrate such cognitive profiles. If, however, the gene itself exerts some influence over brain development, the cognitive differences would most likely be present (and potentially nonprogressive) early in life.

Although overall intellectual function in young children with cystinosis was in the normal range, young children with cystinosis demonstrated a discrepancy such that non-verbal IQ indices (Performance IQ and Processing Speed Index) were significantly lower than verbal IQ indices (17). This pattern closely resembles the IQ profile found previously in older individuals with cystinosis (10) and suggests that the cognitive profile may emerge early in development.

To examine this issue more specifically, the present study tested visual perceptual and visual spatial abilities in very young children with nephropathic cystinosis.

METHODS

Participants

Children with nephropathic cystinosis (n=25; age range 3 years 1 month through 8 years 0 months), and 25 matched control children (age range 3 years 3 months through 7 years 9 months) participated in the study. Children with cystinosis were identified primarily through the National Cystinosis Foundation, the Cystinosis Research Network, and the Cystinosis Research Foundation, all of which maintain close contact with many cystinosis families. Children from many parts of the country were brought to San Diego with a parent to participate in the study. All children had a diagnosis of infantile nephropathic cystinosis confirmed by clinical presentation and by assays documenting elevated leukocyte cystine concentrations. Children were excluded from the study if they were in renal failure, were acutely ill, or had any other condition that might affect cognitive function. Mean age at diagnosis of cystinosis was 17.3 ± 9.6 months; mean age at onset of treatment with cysteamine was 20.7 ± 11.7 months. Renal function data were not available for all patients with cystinosis. However, none were on dialysis at the time of testing, and all parents reported that their children were not in renal failure to their knowledge.

Because of the relatively small sample size and the use of some non-normed tests (or use of data from participants out of the age range of the normative data for some tests), a case-control study design was selected. Control participants were recruited from the community through

advertisements in parent magazines, through local health fairs, and through fliers placed in pediatricians' offices. The cystinosis and control participants were matched for sex, within 8 months of chronological age, and within 1 point for socioeconomic status based on the Hollingshead Four Factor Index of Social Status (18). All controls had normal developmental histories, and no evidence of medical or neurological conditions that might affect cognitive function, such as seizures, head trauma leading to prolonged loss of consciousness, attention deficit-hyperactivity disorder, or learning disabilities.

Informed consent was obtained according to UCSD Human Research Protection Program (HRPP) procedures, and the study was approved by the HRPP. This study was part of a larger longitudinal study of brain structure and cognition in cystinosis.

Cognitive measures

Intelligence—All children received an age-appropriate Wechsler Intelligence Scale (WPPSI-III, WISCIII, or WISC-IV) (19-21). Only 4 children received the WISC-IV (all from the cystinosis group). Since the WISC-IV does not yield verbal IQ (VIQ) or performance IQ (PIQ) scores, the WISC-IV Verbal Comprehension Index was substituted for VIQ and the WISC-IV Perceptual Reasoning Index was substituted for PIQ.

Visual Perception Tasks

Gollin Incomplete Figures (22): This is an object recognition task in which participants are shown incomplete line-drawings of familiar objects presented in five gradations of completeness. The participant must mentally “fill in” missing visual information. For each test item, the most incomplete picture was shown first, for 3 seconds, and the participant was asked to guess what it might be. More pictures in subsequent gradations of completeness were also shown for 3 seconds until the participant was able to correctly identify the object. The test consisted of one practice item followed by 21 test items. The total number of pictures needed to identify all of the items was calculated. The possible range of scores was 21 to 105, with a higher score representing poorer performance.

Motor-Free Visual Perception Test (MFVPT) (23): The MFVPT is a test of visual perception which does not require motor skills. Test items are categorized into five groups including Spatial Relationships, Figure-Ground, Visual Discrimination, Visual Memory, and Visual Closure. Raw scores were used because many of our subjects were below the normative data cutoff (4 years 0 months). The possible range of raw scores was 0 to 36, with higher scores representing better performance.

The Beery-Buktenica Developmental Test of Visual-Motor Integration, 5th Edition (VMI): Visual Perception Supplement (24): The VMI Visual Perception supplement is a test of visual perception without motor requirements that uses smaller versions of the VMI figures as test stimuli. In this task, the participant was required to find the test stimulus among the choices below. Raw scores were converted to standard scores with a mean of 100 and a standard deviation of 15.

Visual Spatial Tasks

Kaufman Assessment Battery for Children (K-ABC): Spatial Memory (25): This test is used to assess short-term spatial recall of simultaneously visually presented material. The participant was shown a page with familiar pictures for 5 seconds, and was then shown an empty grid and asked to point to those boxes on the grid that correspond to the exact positions of the previously shown pictures. Raw scores were used because many of our subjects were below the normative data cutoff (4 years 6 months). The possible range of raw scores was 0 to 21, with higher scores representing better performance.

Woodcock-Johnson: Spatial Relations (26): This is a test of visual spatial ability that does not require motor involvement. The participant was required to select, from a series of shapes, component parts required to make a whole. Raw scores were converted to standard scores with a mean of 100 and a standard deviation of 15.

The Beery-Buktenica Developmental Test of Visual-Motor Integration, 5th Edition (VMI) (24): The VMI is a test of visual motor skills with a visual spatial component (27). The participant was required 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.

Statistical Analyses

Potential group differences (cystinosis versus control) on the demographic variables of age at testing, socioeconomic status, and VIQ were analyzed using t-tests. A Multivariate Analysis of Covariance framework (MANCOVA) was used to analyze the cognitive data. VIQ was chosen as a potential covariate (instead of PIQ or FSIQ), since PIQ (and therefore FSIQ) may be abnormally low because of visual perceptual or visual spatial deficits in the cystinosis group. In the overall between-group analyses, the dependent variables were cognitive test scores and the independent variable was group membership (cystinosis versus control).

RESULTS

The cystinosis and control participants were not significantly different on the demographic variables of age at testing, socioeconomic status, or sex. There was a significant difference between the groups on VIQ, with the cystinosis group scoring in the average range, albeit lower than controls. VIQ was therefore included in the model as a covariate. See Table I for group means, standard deviations, and significance values for the demographic and intelligence variables.

Table II shows the visual perception and visual spatial MANCOVA results, individual test means and standard deviations, estimated marginal means and standard deviations, and significance values. Multivariate analyses indicated that the cystinosis and control groups were not significantly different on any visual perception measures. In contrast, the cystinosis group performed significantly more poorly than did the control group on the visual spatial measures [$F_{(3,45)} = 3.6$, $p = .020$]. Tests of between subjects effects revealed that of the visual spatial tasks, the cystinosis group performed significantly more poorly than the control group on Spatial Relations [$F_{(1,47)} = 5.0$, $p = .031$] and the VMI [$F_{(1,47)} = 7.4$, $p = .009$].

DISCUSSION

We demonstrate a significant impairment in visual spatial and visual motor skills in very young children with nephropathic cystinosis, with a relative sparing of visual perceptual skills. VIQ was lower in the cystinosis group than in controls (although in the average range). Even after co-varying for VIQ, however, the children with cystinosis performed significantly more poorly on visual spatial and visual motor measures than did controls, whereas visual perceptual skills remained intact. These findings are strikingly consistent with previous studies demonstrating impaired performance on visual spatial and visual motor tasks in older children and adults with cystinosis (12,27). Thus, the current results, as well as our recent findings of significantly lower Performance IQ scores on the Wechsler Preschool and Primary Intelligence Scales in younger children (17) argue against progressive cystine accumulation during childhood as the explanation for the observed cognitive differences in cystinosis.

One of the benefits of the current study was that we included a very homogeneous group of children with cystinosis, in that all had been treated from an early age with cysteamine. The

mean time between initiation of treatment with cysteamine and cognitive testing for this study was almost 33 months. Although there is no means of measuring brain cystine levels in living individuals, almost 3 years of treatment would allow reasonable time for cysteamine to have a beneficial effect on tissue cystine levels. If cystine accumulation in the brain were responsible for the cognitive deficits previously observed in older children and adults, as suggested by Broyer (14), we would expect that younger children would exhibit few or no cognitive deficits compared with controls, in particular since early treatment with a cystine-depleting agent had been initiated.

An alternative explanation of the cognitive dysfunction is a very early (possibly in utero) effect on brain development, either from a direct effect of the abnormal cystinosis gene, or as a result of very early deposition of cystine during a critical period of brain development. In this case, the neural changes are not age-dependent in the sense of a cumulative effect of cystine during childhood. The exact mechanism by which cystine damages cells is unknown (4). We speculate that the early neurologic influence of the metabolic disorder might be particularly injurious to brain myelination. A potential mechanism for white matter damage in utero is damage to pre-oligodendroglial cells, the precursors of myelin-forming oligodendroglia. It is known that such cells are susceptible to oxidative stress (28-29) such as might be caused by a metabolic disturbance caused by the defective Cystinosis gene. Defective myelination in turn could adversely affect the development of cortico-cortical projections necessary for complex processing abilities.

A third possibility is that cysteamine, the medication used to clear cystine from the lysosomes, may have some adverse effect on cognitive function. In studies of older children and adults, however, similar results were obtained in patients who had never been given cysteamine (10, 15), suggesting that other factors are more likely responsible for the cognitive deficit.

Lastly, it is possible that renal dysfunction could impair cognitive functioning in the children with cystinosis. None of the children in our study were on dialysis, and parents of all the children reported that their child had normal or near-normal renal function. However, since we do not have specific data on renal function from all of the children at the time of cognitive testing, it is possible that some degree of renal impairment was present that might have contributed to the findings of the present study. Future studies will attempt to ascertain the degree of renal dysfunction in children undergoing these studies.

One of the limitations of the current study is that it is cross-sectional, so that we are unable to compare cognitive performance in the same children over time. Despite this fact, it is reasonable to at least compare our results to those of previous studies of older individuals. Longitudinal studies to more directly address this issue are currently in progress. A second limitation is that we do not as yet have complete structural data from neuro-imaging on these children in order to relate functional differences to brain structural alterations. These studies are underway. However, the results of the current study are suggestive of a very early adverse effect of the cystinosis gene on brain development, such that cognitive function is impaired even in young children with this disorder. The practical implication of this finding is that children with cystinosis may be at risk for learning difficulties (13), particularly in subjects with a significant visual spatial component (e.g., arithmetic, geography). Early identification of specific cognitive deficits will permit prompt remediation in a strongly language-based curriculum, as well as utilization of computer-assisted educational techniques to reduce complications of poor fine motor skills that can make handwriting tedious and illegible.

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Table 1

Summary of demographic variables for the Cystinosis and Control groups.

	Cystinosis (n = 25)	Control (n = 25)	<i>p</i>
Mean Age at Testing	5 yrs. 5 mos. $\pm$ 1 yr. 5 mos.	5 yrs. 4 mos. $\pm$ 1 yr. 3 mos.	NS
Mean Socioeconomic Status *	2.32 $\pm$.90	1.84 $\pm$.94	NS
Sex	13 males, 12 females	13 males, 12 females	---
VIQ	93.40 $\pm$ 12.73	114.00 $\pm$ 12.65	$p < .0001$

* Based on the Hollingshead Four Factor Index of Social Status(Hollingshead, 1975), with 1 being the highest and 5 being the lowest socioeconomic status.

Table 2

Visual perception and visual spatial MANCOVA results, individual test means and standard deviations, estimated marginal means and standard deviations, and significance values.

Multivariate Model and Individual Tests	Mean $\pm$ SD		Significance
	Cystinosis (<i>n</i> = 25)	Control (<i>n</i> = 25)	
Visual Perception MANCOVA			NS
Gollin Incomplete Figures Test Raw Score (<i>Estimated Marginal Mean</i>)	62.2 $\pm$ 10.1 (61.4 $\pm$ 2.3)	55.9 $\pm$ 9.9 (56.7 $\pm$ 2.3)	--
Motor Free Visual Perception Test Raw Score (<i>Estimated Marginal Mean</i>)	18.4 $\pm$ 7.5 (19.4 $\pm$ 1.8)	23.9 $\pm$ 7.7 (22.9 $\pm$ 1.8)	--
VMI: Visual Perception Supplement Standard Score* (<i>Estimated Marginal Mean</i>)	86.2 $\pm$ 17.1 (94.3 $\pm$ 3.1)	109.8 $\pm$ 15.7 (101.7 $\pm$ 3.1)	--
Visual Spatial MANCOVA			p = .02
K-ABC Spatial Memory Raw Score (<i>Estimated Marginal Mean</i>)	5.0 $\pm$ 4.1 (5.4 $\pm$ 1.0)	8.3 $\pm$ 4.2 (7.9 $\pm$ 1.0)	NS
Woodcock Johnson Spatial Relations Standard Score* (<i>Estimated Marginal Mean</i>)	97.6 $\pm$ 18.1 (100.6 $\pm$ 3.2)	115.1 $\pm$ 9.1 (112.1 $\pm$ 3.2)	p = .031
VMI Standard Score* (<i>Estimated Marginal Mean</i>)	84.0 $\pm$ 12.2 (87.6 $\pm$ 2.9)	103.5 $\pm$ 13.7 (100.0 $\pm$ 2.9)	p = .009

Note: -- represent subtests for which follow-up analyses were not applicable because the multivariate test was not significant.

* represents tests for which VIQ was a significant covariate