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Cognition in Nephropathic Cystinosis: Pattern of Expression in Heterozygous Carriers

Stephen Niemiec^{1,2}, Angela Ballantyne², and Doris Trauner^{2,3,4}

¹Johns Hopkins University

²Department of Neurosciences, University of California San Diego School of Medicine

³Department of Pediatrics, University of California San Diego School of Medicine

⁴Rady Children's Hospital San Diego

Abstract

Individuals with cystinosis exhibit specific cognitive deficits in visual spatial function. The purpose of the current study was to examine if obligate heterozygotes of the CTNS mutation have the same pattern of cognitive functioning seen in homozygotes, namely aberrant visual-spatial functioning against a background of relatively intact visual-perceptual functioning and overall cognitive ability. Study participants were 254 adults (100 heterozygotes and 154 controls), ages 17 years 10 months through 74 years 9 months. Tests of intelligence, visual perceptual, and visual spatial functioning were administered. Our results showed that cystinosis heterozygotes demonstrated intelligence within the normal range, and performed similarly to controls on tests of visual-perceptual ability. In contrast, the heterozygotes performed significantly more poorly on each of the visual-spatial tests when compared to controls. Obligate heterozygotes for the CTNS mutation display a similar pattern of visual processing decrements as do individuals with cystinosis. Namely, carriers demonstrate relative weaknesses in visual-spatial processing, while maintaining normal visual perceptual ability and intelligence in the normal range. The visual spatial decrements in heterozygotes were not as marked as those found in individuals with cystinosis, suggesting a gene dosing effect. This study provides an impetus for other studies of gene-behavior relationships in recessive disorders, and may stimulate further interest in the role of aberrant genes on “individual differences” in behavior.

Keywords

Cystinosis; heterozygotes; visual spatial function

INTRODUCTION

Nephropathic cystinosis is an autosomal recessive disorder of cystine transport. Cystinosis affects between 1 in 100,000 and 1 in 200,000 live births [Gahl et al., 2002]. Individuals with cystinosis have a mutation on chromosome 17p13 in the Cystinosin (CTNS) gene, which codes for cystinosin, a lysosomal membrane transport protein [Cystinosis Collaborative Research Group, 1995; McDowell et al., 1996; Sholtelsuk et al., 1998; Town et al., 1998; Anikster et al., 1999]. As a result, the amino acid cystine accumulates

Corresponding Author and Reprint Requests: Doris A. Trauner M.D. Department of Neurosciences UCSD School of Medicine 9500 Gilman Drive La Jolla CA 92093-0935 USA dtrauner@ucsd.edu Telephone: 858-822-6700 Fax: 858-822-6707.

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within the lysosomes in all cells of the body leading to complications of the renal tubular Fanconi Syndrome. Cystinosis, when untreated, is characterized by progressive renal failure leading to renal transplantation by 10 to 12 years of life [Gahl et al., 2001]. There have been a large number of mutations in CTNS identified, with the most common being a 57-kb deletion involving most of the CTNS gene [Cystinosis Collaborative Research Group, 1995; Sholtellersuk et al., 1998; Touchman et al., 2000]. Individuals with cystinosis have leukocyte cystine levels 50 to 100 times greater than those of normal individuals. Cystinosis carriers (heterozygotes) also demonstrate defects in the transport of cystine, though to a much lesser extent, with leukocyte cystine levels approximately 6 times greater than normal [Gahl et al., 1984; Smolin et al., 1987].

The successful use of renal transplantation and more recently cysteamine, a cystine-depleting drug, have helped to greatly extend the life spans of patients with cystinosis [Kleta and Gahl, 2004; Soliman et al., 2009; Gahl, 2003]. With longer life expectancy after treatment, long-term effects of cystinosis on the central nervous system (CNS) have been documented. Studies have shown abnormally high levels of cystine and cystine crystal deposits in various regions of the brain [Levine and Paparo, 1982; Broyer and Tete, 1999; Jonas et al., 1987; Vogel et al., 1990; Theodoropoulos et al., 1993]. A specific cognitive profile has been found that includes visuospatial processing deficits on a background of normal intelligence and normal visual perceptual functioning [Trauner et al., 1988; Williams et al., 1994; Ballantyne and Trauner, 2000]. These cognitive impairments are seen in adults and teenagers [Trauner et al., 1988; Ballantyne and Trauner, 2000; Nichols et al., 1990; Fink et al., 1989], as well as young children [Trauner et al., 2007] with cystinosis.

The specific cause of the cognitive profile in patients with cystinosis is unclear. Possible causes include cystine accumulation in the brain or an effect of the underlying gene mutation resulting in differences in brain development [Trauner et al., 1988; Williams et al., 1994; Ballantyne and Trauner, 2000; Nichols et al., 1990; Fink et al., 1989; Trauner et al., 2007]. A recent research study utilizing magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) of the brains of children with cystinosis [Bava et al., 2010] suggests that both mechanisms may play a role in the cognitive differences seen in this disorder. Homozygotes possessed early white-matter changes in the parietal regions of the brain, perhaps impacting the efficiency of fiber networks, particularly in the dorsal processing stream (visuospatial processing networks). There was also evidence of a secondary, ongoing neurobiological process, whereby cystine accumulation over time may have directly or indirectly led to cell degeneration [Hoffmann et al., 1994; Kolker et al., 2002; Di Rocco et al., 2004; Bava et al., 2010]. Regardless of the mechanism, a question remains as to whether cystinosis heterozygotes (carriers) exhibit a similar pattern of cognitive functioning, as these individuals display abnormal cystine transport as well, albeit to a lesser extent than do homozygotes.

The present study was designed to examine if obligate heterozygotes of the CTNS mutation have the same pattern of cognitive functioning seen in homozygotes, namely visual-spatial impairments against a background of relatively intact visual-perceptual functioning and overall cognitive ability. To examine this issue, the current study evaluated overall IQ, visual perceptual and visual spatial abilities in heterozygotes for the CTNS mutation using the same (or similar) cognitive tests as performed in previous studies on individuals with cystinosis [Trauner et al., 1988; Scarvie et al., 1996; Ballantyne and Trauner 2000; Trauner et al., 2007].

METHODS

Participants

Study participants were 100 parents of children with cystinosis (thus obligate heterozygotes, or “carriers”) and 154 adult controls. The carrier group (56 females, 44 males) ranged in age from 22 years 11 months to 74 years 9 months, and the control group (87 females, 67 males) ranged in age from 17 years 10 months to 69 years. Due to time constraints, some subjects did not complete all tests. Importantly, none of the carriers exhibited any symptoms of cystinosis, including no evidence of corneal crystals, renal dysfunction, or any other indications of having a sub-clinical disease state.

Cystinosis parents were recruited for the study at cystinosis family conferences or when parents brought their children to the University of California – San Diego (UCSD) for other studies. Control participants were recruited from the community through newspaper advertisements and fliers. All control participants had normal developmental and medical histories, with no indication of a neurological condition that might affect cognition.

Informed consent was obtained following UCSD Human Research Protection Program procedures. The study was approved by the Human Research Protection Program.

Cognitive Measures

Intelligence—Stanford-Binet Intelligence Scale, Fourth Edition [Thorndike et al., 1986]: The Stanford-Binet Intelligence Scale was used to test Verbal Reasoning, Abstract/Visual Reasoning, Quantitative Reasoning, and Short-Term Memory. A composite IQ was calculated using 5 subtests: Vocabulary, Pattern Analysis, Quantitative Analysis, Bead Memory, and Memory for Sentences. The test is standardized across a large age range from toddler to adulthood (2-23 years). Adults older than the normative data range were scored using the highest age-norms available. Moreover, we had a similar age range in controls and heterozygotes in order to reduce any potential differences in IQ with ages outside of the standard range. The subtests have a standard mean of 50 and $SD \pm 8$, and the Composite Score is standardized with a mean of 100 and $SD \pm 16$.

Visual Perception Tasks—Gollin Incomplete Figures [Gollin, 1960]: This is an object recognition task in which the participants must “fill in” missing visual information in incomplete line drawings of recognizable objects presented in five increasing levels of completeness. The participant was shown the most incomplete drawing for 3 seconds and asked to identify it. Each gradation of the picture was shown for 3 seconds until the subject correctly guessed the familiar object. The participants were given 1 practice item followed by 21 test drawings. The subject's score was calculated using the number of total pictures required to identify all 21 test items, with a possible range of scores between 21 and 105, with higher scores representing poorer performance.

Stanford-Binet Intelligence Scale, Fourth Edition, Memory for Objects subtest [Thorndike et al., 1986]: This is a test of memory without a spatial component. Participants were shown a series of common objects, one at a time. They were then required to choose the previously shown items in their order of appearance from a sheet containing a larger array of pictures. Standard scores were calculated by age with a mean of 50 and $SD \pm 8$.

Visual Spatial Tasks—Locomotor Maze [Semmes et al., 1955]: This is a task of extrapersonal orientation that required participants to direct themselves through a series of paths given on 5 different maps. The test room was designed with nine “landmarks” and a wall labeled “North,” which are depicted on each map along with a path between the

landmarks. The subject started at the “South” wall and was asked to walk through a path on the floor as indicated by the path on their map. The map was not always given to the participant in the proper orientation with respect to extrapersonal space and the subject was asked not to turn the map. The participant received detailed instructions and two practice tasks before participating in the actual test items. The subjects were measured on the total time it took to complete all five maps.

Woodcock-Johnson: Spatial Relations [McGrew and Woodcock, 1985]: This is a test of visual-spatial ability requiring no motor involvement. Participants were required to select, from a series of shapes, component parts required to make a whole. Standard scores were calculated with a mean of 100 and a SD of 15. The test is normed from 2 to 90+ years.

Space Thinking – Flags [Thurstone and Jeffries, 1956]: This is a test of spatial orientation. The participant was given 21 multiple-choice drawings, each composed of a “flag,” a rectangular geometric design, and six designs that mirror the “flag,” differ in spatial rotation, or both. The subject was instructed to circle “S” if the design matched the “flag” or “O” if the design was a mirror of it. The test has a 5-minute time limit. Standardized T scores were calculated with a mean of 50 and $SD \pm 10$.

Stanford-Binet Intelligence Test, Fourth Edition, Bead Memory Subtest [Thorndike et al., 1986]: This subtest is a test of visual short-term memory with a spatial component [Trauner et al., 1988]. Participants were shown a picture with beads of different colors and shapes placed in a certain order and orientation on a stick. After being shown the picture for 5 seconds, the participant was asked to re-create it. Scores were converted into standard scores based on age with a mean 50 and $SD \pm 8$.

Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), 5th Edition [Beery and Beery, 2004]: This was used to test visual spatial and visual motor abilities without involving a memory component. The participant was required to copy geometric figures that gradually increased in complexity. Standard scores were calculated with a mean of 100 and a SD of 15. The test is normed from 2-18 years.

Analyses were conducted to determine whether the carrier group performed more poorly than the control group on the general cognitive, visual perceptual, and visual spatial tasks, utilizing one-tailed tests of significance. Statistical procedures used were the Student's t-test for standard scores and the Mann-Whitney U Test for non-standardized tests. When standard scores were not available, ages were matched so the mean age was not significantly different between the control and heterozygote groups. We used linear regression analyses to study the effect of age on cognitive test scores.

RESULTS

Demographics

Because not all participants were administered all tests, the cognitive measures were examined independently for relevant demographic variables of age and gender. The Stanford-Binet Intelligence Scale—4th Edition, Stanford-Binet Memory for Objects Subtest, Woodcock-Johnson Spatial Relations, Space Thinking – Flags, and Beery-Buktenica Developmental Test of VMI all use standardized scores and there was no significant difference in sex ratio between the groups. Ages were matched for the remaining two non-standardized tests, and the mean and SD of age are presented in Table I.

Since there was a large age range for both heterozygote and control groups, we performed linear regression analyses with test result by age. These showed no indication of an influence of age on test scores for either group.

Intelligence

The results of the Stanford-Binet Intelligence Scale are shown in Table II. Both the controls and the heterozygotes had a mean IQ well within the normal range, although the heterozygotes scored significantly lower than the controls on each subtest except for Pattern Analysis. However, only Bead Memory had a mean result below the expected mean for the test in the heterozygote group (see Fig 1).

Visual Perception Tasks

Table III shows the mean, SD and p-value for each of the visual processing tasks. No significant difference between heterozygotes and controls was found on any of the visual perception tests given.

Visual Spatial Tasks

The mean performance of the heterozygote and control groups on each of the visual spatial tests is shown in Table IV. The heterozygote group performed significantly more poorly than the control group on all of the visual spatial tasks: Locomotor Maze ($p = .009$), Spatial Relations ($p = .0035$), Space Thinking ($p = .027$), and VMI ($p = .0035$) (see Figs 2-4).

DISCUSSION

Results of the current study indicate that parents of children with nephropathic cystinosis, who are obligate heterozygotes for the CTNS mutation, display a similar pattern of visual processing decrements as do individuals with cystinosis, who are homozygous for the CTNS mutation. Namely, carriers demonstrate relative weaknesses in visual-spatial processing, while maintaining normal visual perceptual ability and intelligence in the normal range.

The heterozygotes performed significantly more poorly on each of the visual spatial tests when compared to controls, but displayed no significant differences in visual perceptual function. Heterozygote IQ was well within the normal range, though still lower than expected based on the performance of controls. However, only the visual spatial memory task (Bead Memory subtest) was below the population mean, while all other subtest scores of the Stanford Binet were at or above the population mean in the heterozygotes. Thus, this does not represent merely a general defect in cognition, but rather a specific pattern of visual spatial dysfunction. This particular pattern of visual spatial, visual perceptual, and IQ functioning has been seen in numerous studies of individuals with cystinosis [Williams et al., 1994; Ballantyne and Trauner, 2000; Spilkin et al., 2007; Trauner et al., 2007; Ulmer et al., 2009; Besouw et al., 2010], yet the degree of decrement in heterozygotes appears to be attenuated. For example, when standard scores from the current study are compared with those reported in previous studies on cystinosis patients [Trauner et al., 1988; Spilkin et al., 2007; Trauner et al., 2007], the cystinosis mean score versus the carrier mean score is 91 vs. 106 for IQ; 98 vs. 101 for Spatial Relations; 84 vs. 88 for VMI; 43 vs. 48 for Bead Memory. Although the heterozygote group's visual spatial scores are not impaired per se, they do fall between the mean scores of the control and the homozygote groups.

In summary, as in individuals with cystinosis, it appears that heterozygous carriers of the cystinosis gene also demonstrate a pattern of lower than expected visual spatial processing compared with visual perceptual ability and global intellectual function. It is widely known that visual-spatial and visual-perceptual functions may be mediated by different

neuroanatomic pathways, and deficits may be seen in one visual processing area but not the other [Ungerleider and Mishkin, 1982; Goodale and Milner, 1992; Benton and Tranel, 1993; Milner and Goodale, 1995]. Moreover, the selective vulnerability of visual-spatial (dorsal-stream) functions is seen in a number of other neurological and genetic disorders including Williams syndrome, fragile X, Turner syndrome, velo-cardio facial syndrome, and Alzheimer disease [Butter et al., 1996; Bearden et al., 2001; Maurice et al., 2009; Atkinson and Braddick, 2011]. Interestingly, a recent study of the central nervous system and behavior in a mouse-model of cystinosis [Maurice et al., 2009] showed differential concentrations of cystine depending on the brain structure studied, and behavioral findings that paralleled those we have seen in the cystinosis population [Trauner et al., 1988; Nichols et al., 1990; Williams et al., 1994; Scarvie et al., 1996; Ballantyne and Trauner, 2000]. Bava et al. [2010], in a recent brain-imaging study using diffusion tensor imaging of cystinosis patients, found reduced brain white-matter integrity, particularly of the dorsal stream. Our findings thus indicate that in asymptomatic carriers of this recessive gene disorder, there may be a concentration-dependent effect of the gene on neurocognitive function. At this time, it is unknown whether this may be due primarily to early neurodevelopmental brain changes, with a secondary effect of ongoing neurobiological insult from cystine accumulation, as suggested by Bava et al.'s [2010] findings in cystinosis patients. In a study of asymptomatic carriers of the gene for Machado-Joseph disease [Soong and Liu, 1998], "preclinical" metabolic changes in the brain were detected by PET scans. Studies of the effect of "asymptomatic carrier genes" on individual differences in brain and cognition are rare, yet intriguing.

This study has implications not only for the effect of heterozygosity for the CTNS mutation on cognitive function, but more broadly for other recessive disorders. Carriers of other autosomal recessive disorders may possess subtle cognitive "differences" caused by an abnormal gene copy. The results of this study provide an impetus for other studies of gene-behavior relationships in recessive disorders, and may stimulate further interest in the role of aberrant genes on "individual differences" in behavior.

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Figure 1. Comparison of Heterozygote and Control group performance on Stanford-Binet subtests. Higher scores indicate better performance. The average standard score for each test is 50. Cystinosis carriers performed significantly more poorly than controls on all subtests ($p < 0.05$) except Pattern Analysis.

Figure 2. Comparison of Heterozygote and Control group performance on the Locomotor Maze test. Longer time indicates poorer performance. Carriers performed significantly more poorly than controls ($p = .009$).

Figure 3. Comparison of Heterozygote and Control group performance on Woodcock-Johnson Spatial Relations. Carriers performed significantly more poorly than controls ($p = .0035$), although within normal range.

Figure 4.
Comparison of Heterozygote and Control group performance on Space Thinking - Flags.
Cystinosis carriers performed significantly more poorly than controls ($p = .027$).

Table I

Age demographics for participants in non-standardized tests

Test	Age (Mean $\pm$ SD, yrs)		Significance
	Parents (Carriers)	Controls	
Gollin Incomplete Figures	38.5 $\pm$ 8.9	38.1 $\pm$ 9.2	NS
Locomotor Maze	39.3 $\pm$ 9.7	36.4 $\pm$ 7.9	NS

Table II

Performance of adult cystinosis carriers and adult controls on selected subtests of the Stanford-Binet Intelligence Scale, Fourth Edition

Subtest	Mean $\pm$ SD, (n)		Significance
	Parents (Carriers)	Controls	
Vocabulary	55.7 $\pm$ 7.4, (93)	59.1 $\pm$ 7.0, (117)	.0005
Pattern Analysis	52.9 $\pm$ 4.6, (92)	53.0 $\pm$ 5.0, (117)	NS
Quantitative Analysis	52.3 $\pm$ 6.9, (91)	55.3 $\pm$ 7.0, (117)	.002
Bead Memory	47.8 $\pm$ 6.4, (93)	51.3 $\pm$ 6.7, (115)	<.0001
Memory for Sentences	50.4 $\pm$ 7.4, (92)	52.7 $\pm$ 8.2, (116)	.016
Composite	105.6 $\pm$ 10.6, (93)	111.1 $\pm$ 11.0, (115)	.0002

Table III

Performance of adult cystinosis carriers and adult controls on selected visual perception tests.

Test	Mean $\pm$ SD, (n)		Significance
	Parents (Carriers)	Controls	
Gollin Incomplete Figures (raw score)	32.0 $\pm$ 4.4, (69)	31.3 $\pm$ 4.2, (51)	NS
Memory for Objects (standard score)	50.7 $\pm$ 6.5, (53)	52.2 $\pm$ 6.9, (54)	NS

Table IV

Performance of adult cystinosis carriers and adult controls on selected visual spatial tests.

Test	Mean $\pm$ SD, (n)		Significance
	Parents (Carriers)	Controls	
W-J Spatial Relations (Standard Score)	100.9 $\pm$ 12.6, (74)	106.5 $\pm$ 13.4, (88)	.004
Space Thinking Flags (Standard Score)	47.5 $\pm$ 6.7, (68)	50.0 $\pm$ 8.7, (78)	.027
Locomotor Maze Time to Complete	175.9 $\pm$ 73.4, (44)	141.0 $\pm$ 46.2, (25)	.033
VMI (Standard Score)	88.3 $\pm$ 10.5, (78)	92.3 $\pm$ 8.3, (78)	.004