Non-Verbal Deficits in Young Children With a Genetic Metabolic Disorder: WPPSI-III Performance in Cystinosis

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Cystinosis is a recessive genetic metabolic disorder in which the amino acid cystine accumulates in various organs of the body. Previous studies have demonstrated visuospatial dysfunction in children and adults with this disorder. It is not known whether this is a result of the genetic alteration or an accumulation of cystine in the brain over time. This study investigated patterns of performance in 20 young children with cystinosis (4–7 years) and 20 matched controls on the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III). The children with cystinosis had a mean Full Scale IQ at the low end of the average range. Their overall cognitive functioning was comprised of average verbal abilities, low average non-verbal abilities, and low average processing speed. Multivariate analyses indicated that the cystinosis and control groups were not significantly different on the verbal subtests. In contrast, the cystinosis group performed significantly more poorly than controls on the performance and processing speed subtests. Although overall intellectual function was in the normal range, young children with cystinosis demonstrated a discrepancy such that non-verbal abilities were poorer relative to verbal abilities. This pattern resembles the cognitive profile found previously in older individuals with cystinosis and indicates that the specific cognitive profile emerges early in development. These findings suggest that the cognitive dysfunction in cystinosis is not merely the result of cystine accumulation over time but may be related to differences in brain development as a consequence of alterations or deletions of the cystinosin gene. © 2007 Wiley-Liss, Inc.

KEY WORDS: cystinosis; IQ; visuospatial; brain development

INTRODUCTION

Infantile nephropathic cystinosis is a rare autosomal recessive disorder in which the amino acid cystine accumulates in the lysosomes. The organ affected most severely early in life is the kidney, but most other organs are affected as well [Gahl et al., 2001]. Neuroimaging and neuropathological studies of individuals with cystinosis have demonstrated central nervous system (CNS) involvement, including cerebral atrophy, white matter necrosis, patchy demyelination, and brain cystine accumulation [Ehrich et al., 1979; Levine and Paparo, 1982; Ross et al., 1982; Cochat et al., 1986; Gahl and Kaiser-Kupfer, 1987; Jonas et al., 1987; Fink et al., 1989; Nichols et al., 1990; Vogel et al., 1990].

Studies examining cognitive functioning in individuals with cystinosis have shown overall intelligence within the normal range as well as average performance in the areas of language and auditory processing [Nichols et al., 1990]. In contrast, individuals with cystinosis perform more poorly than controls on tests of visual memory [Trauner et al., 1988] and visual-motor integration [Scarvie et al., 1996]. Recent studies have demonstrated specific deficits in visuospatial functioning, whereas visual perceptual skills remain intact [Ballantyne and Trauner, 2000].

Although global intellectual function is within the normal range [Fink et al., 1989], IQ is lower than would be predicted based on the IQs of siblings and parents [Williams et al., 1994]. Academically, individuals with cystinosis exhibit poorer performance than comparison groups on arithmetic and spelling [Williams et al., 1994; Ballantyne et al., 1997].

There are at least two potential mechanisms that might explain the previously observed cognitive profile. The underlying gene mutation might exert an adverse effect on early brain development, resulting in neural changes that could account for differences in cognitive functioning. In this instance, one would expect the cognitive deficits to be present early in life, and to be relatively stable over time. Alternatively, progressive accumulation of cystine within the brain during childhood could lead to cognitive impairments. If this hypothesis were correct, one would anticipate that these children would demonstrate no or mild cognitive differences early in life, with progressive worsening over time.

To begin to elucidate the potential mechanism of cognitive impairment in cystinosis, the current study examined cognitive functioning in a *very young* group of children. The aim of the current study was to determine whether the cognitive profile previously found in school-age children and adults with cystinosis is present in young children. We examined results from the Wechsler Preschool and Primary Scale of

Intelligence-Third Edition (WPPSI-III) [Wechsler, 2002]. It was hypothesized that children with cystinosis would exhibit verbal and overall intellectual abilities (VIQ and FSIQ) in the normal range, with relative deficits in performance IQ (PIQ) because many of the non-verbal tasks on the PIQ scale involve visuospatial ability.

METHOD
Participants

Participants were 20 children with cystinosis (mean age 5 years 0 months, range 4-0 to 7-0) and 20 typically developing control subjects (mean age 5 years 5 months, range 4-0 to 7-1). Participants with cystinosis were diagnosed by a nephrologist or metabolic disorders specialist based on clinical history and laboratory confirmation (i.e., elevated leukocyte cystine levels). Individuals with cystinosis were excluded from the study if they had impaired vision, had uncorrected thyroid problems, or were in renal failure. All children in the study were taking cysteamine (Cystagon) at the time of testing. The dose range reported was 50–60 mg/kg/day in four equally divided doses. All children were taking electrolyte replacement supplements as well. In addition, there were a number of medications reportedly being taken by some of the children in the study. These included L-carnitine (8); omeprazole (Prilosec; 3); esomephrazole (Nexium; 3); metoclopramide (Reglan; 3); lansoprazole (Prevacid; 2); growth hormone replacement therapy (2); indomethacin (1); Singulair (1); lisinopril (1); chlorothiazide (1); and dihydrotachysterol (DHT; 1). We were unable to obtain laboratory testing on all of the children in the study. Parents reported, however, that their children had "good" to "acceptable" renal function and were metabolically in good balance based on their physicians' communications with them. No child was ill or known to have significant renal or other metabolic dysfunction at the time of the study.

Control participants had normal developmental and medical histories and were recruited from the community through advertisements and physician referrals. All participants were part of a larger longitudinal study examining brain structure and cognition in children with cystinosis. Informed consent was obtained in accordance with UCSD Institutional Review Board procedures.

Measure

The WPPSI-III is a commonly used measure of intelligence in young children ages 2–6 to 7–3 years. It consists of subtests that represent verbal skills, performance skills, and processing speed, as well as composite scores that represent Verbal IQ (VIQ), Performance IQ (PIQ), a Processing Speed Quotient (PSQ), and Full Scale IQ (FSIQ). The Core subtests of the WPPSI-III for children ages 4-0 to 7-3 years are: Information, Vocabulary, and Word Reasoning (Verbal Scale); Block Design, Matrix Reasoning, and Picture Concepts (Performance Scale), and Coding (Processing Speed Quotient). Although not a core subtest for FSIQ, Symbol Search was also administered

allowing the computation of the Processing Speed Quotient. Each subtest has a mean score of 10 ± 3, and the composite scores of VIQ, PIQ, PSQ, and FSIQ have a mean of 100 ± 15.

Analyses

Between-group (cystinosis vs. control) analyses of VIQ, PIQ, PSQ, and FSIQ were conducted using independent samples t-tests. To compare subtest scores between the groups, a multivariate framework was used. Multivariate Analyses of Variance (MANOVAs) for the Verbal, Performance, and Processing Speed subtests were conducted separately. To further characterize the pattern of performance by the cystinosis group, all WPPSI-III Composite Scores and subtest scores were compared to the normative means using one-sample t-tests.

RESULTS
Comparison of Cystinosis and Control Groups

Cystinosis and control children were not significantly different on the demographic variables of socioeconomic status or age at testing. Compared to age- and SES-matched controls, the cystinosis group performed significantly more poorly on VIQ, PIQ, PSQ, and FSIQ (see Table I). Qualitatively, the cystinosis group performed in the Average range on VIQ and FSIQ and in the Low Average range on PIQ and PSQ, whereas the control group performed in the Average range across all composite indices.

Multivariate analyses indicated that the cystinosis and control groups were not significantly different on the WPPSI-III verbal subtests (Table II). In contrast, the cystinosis group performed significantly more poorly than did the control group on the performance subtests and the processing speed subtests. Follow-up analyses revealed that on the subtests of Block Design, Matrix Reasoning, Symbol Search, and Coding, the cystinosis group performed significantly more poorly than the control group. The cystinosis group performed in the Average range on the verbal subtests and in the Low Average range on the performance and processing speed subtests (with the exception of Picture Concepts).

Comparison of Cystinosis Group to Normative Mean

In the cystinosis group, VIQ was not significantly different from the normative mean, whereas PIQ, PSQ, and FSIQ fell significantly below the mean. Similarly, children with cystinosis did not score significantly below the normative mean on any of the verbal subtests, but did score significantly below the mean on all of the non-verbal and processing speed subtests, with the exception of Picture Concepts.

DISCUSSION

The purpose of the present study was to examine intellectual functioning in a young group of children with cystinosis in

TABLE I. Mean WPPSI-III Verbal IQ, Performance IQ, Processing Speed Quotient, and Full Scale IQ, Significance Values, and Qualitative Descriptions for the Cystinosis and Control Groups

WPPSI-III Composite Scales	Mean ± SD			Qualitative Description	
	Cystinosis (n = 20)	Control (n = 20)	Significance	Cystinosis (n = 20)	Control (n = 20)
Verbal IQ	96.25 ± 10.7	107.30 ± 13.9	$P = 0.008$	Average	Average
Performance IQ	89.00 ± 12.9	107.00 ± 15.1	$P < 0.0001$	Low average	Average
Processing Speed Quotient	88.35 ± 10.7	103.50 ± 11.6	$P < 0.0001$	Low average	Average
Full Scale IQ	90.85 ± 10.8	107.50 ± 14.1	$P < 0.0001$	Average	Average

TABLE II. WPPSI-III Overall Verbal, Performance, and Processing Speed MANOVA Results, Individual Subtest Means and Standard Deviations, Significance Values, and Qualitative Descriptions

Multivariate Tests and WPPSI-III Subtests	Mean ± SD		Significance	Qualitative Description	
	Cystinosis (n = 20)	Control (n = 20)		Cystinosis (n = 20)	Control (n = 20)
Verbal MANOVA			NS		
Information	9.30 ± 2.5	10.45 ± 3.4	—	Average	Average
Vocabulary	9.65 ± 2.4	11.15 ± 2.7	—	Average	Average
Word Reasoning	9.50 ± 2.4	11.95 ± 2.9	—	Average	Average
Performance MANOVA			$P < 0.0001$		
Block Design	7.85 ± 2.8	11.50 ± 2.9	$P < 0.0001$	Low average	Average
Matrix Reasoning	7.35 ± 3.1	11.30 ± 3.4	$P < 0.0001$	Low average	Average
Picture Concepts	9.80 ± 3.1	10.75 ± 3.3	NS	Average	Average
Processing Speed MANOVA			$P = 0.001$		
Symbol Search	7.90 ± 2.6	11.00 ± 2.6	$P = 0.001$	Low average	Average
Coding	8.05 ± 2.2	10.50 ± 2.7	$P = 0.003$	Low average	Average

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

order to help define the mechanism of impairment previously observed in older children and adults with cystinosis. Our results indicate that as a group, young children with cystinosis (ages 4–7 years) have a mean IQ at the low end of the average range, which is lower than would be expected compared to age- and SES-matched controls. This result is a composite of average verbal abilities, low average non-verbal abilities, and low average processing speed. The lower than expected Full Scale IQ is largely the result of low Performance IQ, indicating that there is a dissociation between verbal and non-verbal abilities. This pattern replicates, in a *much younger group* of children, findings from older children and adults with cystinosis on other tests of intellectual and cognitive functioning [Trauner et al., 1988; Williams et al., 1994; Scarvie et al., 1996; Ballantyne and Trauner, 2000].

Examination of the WPPSI-III subtests revealed that on the verbal scale subtests, the cystinosis group performed similarly to the control group. In contrast, on the subtests that comprise the performance and processing speed scales, the cystinosis group performed at a significantly lower level than did controls, and predominantly in the low average range. The one performance subtest on which the cystinosis and control groups performed similarly was Picture Concepts. Examination of the normative data for the WPPSI-III, however, demonstrates that Picture Concepts loads more highly on the verbal factor (factor loading = 0.34) than on the performance factor (factor loading = 0.22), suggesting a strong verbal component to the Picture Concepts subtest [Sattler and Dumont, 2004]. Given the intact verbal abilities of our cystinosis subjects, one would expect average performance on this subtest.

To our knowledge, this is the first study of cognitive performance in such a young group of children with cystinosis. Our data indicate that even early in life, individuals with cystinosis are demonstrating the aberrant cognitive profile of non-verbal deficits against a background of average verbal abilities. This suggests that there is an *early* effect of cystinosis on cognitive abilities, and thus possibly on the developing nervous system. The neurologic basis of the observed cognitive profile is unknown, although several possibilities exist. First, the underlying gene mutation might cause a difference in the way the brain develops in utero, resulting in differences in neural or cerebral organization for particular structures and/or functions. Alternatively, progressive accumulation of cystine within the brain during infancy and childhood could lead to the observed cognitive impairments. The results of the current study suggest that the first hypothesis may be more

likely. These children were all being treated with cysteamine, a cystine-depleting agent, at the time of testing, reducing the likelihood of significant cystine accumulation in the brain. Longitudinal studies of cognition in children with cystinosis will help to further define the likely mechanisms of cognitive impairment in nephropathic cystinosis. If the cognitive differences are caused by early changes in brain development, we would expect the cognitive difference to be stable over time. On the other hand, if the cognitive dysfunction is caused by accumulation of cystine in the brain, we would expect the cognitive deficits to worsen over time. These longitudinal studies are in progress.

There are other factors that might explain the observed deficits. One is the medications that the children with cystinosis are taking. All of the children were taking cysteamine. Studies have shown that rats injected with cysteamine show visual memory and locomotor deficits [Fitzgerald and Dokla, 1989; Justino et al., 1997]. Our behavioral data collected across many years, however, indicates that individuals with cystinosis who were never treated with cysteamine show the same cognitive pattern as seen in our current sample [Trauner et al., 1988]. This argues against cysteamine as the sole cause of the impairments. The only other consistent therapies were those involving electrolyte replacements. Most of the other medications listed were taken by a small percentage of the children. Thus it is unlikely that the cognitive results we observed could be caused by one of these medications. Similarly, the children were in good health with no evidence of renal failure or severe metabolic dysfunction, making it unlikely that these might be the explanation for the observed test results.

This study has implications for a greater understanding of the mechanism of cognitive dysfunction observed in these individuals. The pattern of cognitive impairment observed in young children with cystinosis suggests that cystinosis may have a deleterious neurodevelopmental effect on the brain, such that even very young children with the disease show the characteristic cognitive profile. Hence, the timing of the CNS insult in cystinosis may be earlier than previously thought, and may reflect some abnormality in brain development, rather than a long-term cumulative process.

REFERENCES

Ballantyne AO, Trauner DA. 2000. Neurobehavioral consequences of a genetic metabolic disorder: Visual processing in infantile nephropathic cystinosis. Neuropsychiatry Neuropsychol Behav Neurol 13(4):254−263.

Ballantyne AO, Scarvie KM, Trauner DA. 1997. Academic achievement in individuals with infantile nephropathic cystinosis. Am J Med Genet 74:157−161.

Cochat P, Drachman R, Gagnadoux M-F, Pariente D, Broyer M. 1986. Cerebral atrophy and nephropathic cystinosis. Arch Dis Child 61:401−403.

Ehrich JHH, Stoeppler L, Offner G, Brodehl J. 1979. Evidence for cerebral involvement in nephropathic cystinosis. Neuropadiatric 10(2):128−137.

Fink JK, Brouwers P, Barton N, Malekzedah MH, Sato S, Hill S, Cohen WE, Fivush V, Gahl WA. 1989. Neurological complications in long-standing nephropathic cystinosis. Arch Neurol 46:543−548.

Fitzgerald LW, Dokla CPJ. 1989. Morris water task impairment and hypoactivity following cysteamine-induced reductions of somatostatin-like immunoreactivity. Brain Res 505:246−250.

Gahl WA, Kaiser-Kupfer MI. 1987. Complications of nephropathic cystinosis after renal failure. Pediatr Nephrol 1:260−268.

Gahl WA, Thoene JG, Schneider JA. 2001. Cystinosis: A disorder of lysosomal membrane transport. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited diseases, 8th edition. New York: McGraw-Hill. pp 5085−5108.

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.

Justino L, Welner SA, Tannenbaum GS, Schipper HM. 1997. Long-term effects of cysteamine on cognitive and locomotor behavior in rats: Relationship to hippocampal glial pathology and somatostatin levels. Brain Res 761:127−134.

Levine S, Paparo G. 1982. Brain lesions in a case of cystinosis. Acta Neuropathol 57:217−220.

Nichols S, Press GA, Schneider JA, Trauner DA. 1990. Cortical atrophy and cognitive performance in infantile nephropathic cystinosis. Pediatr Neurol 6(6):379−381.

Ross DL, Strife F, Towbin R, Bove KE. 1982. Nonabsorptive hydro-cephalus associated with nephropathic cystinosis. Neurology 32:1330−1334.

Sattler JM, Dumont R. 2004. Assessment of Children: WISC-IV and WPPSI-III Supplement. San Diego, CA: Jerome M. Sattler.

Scarvie KM, Ballantyne AO, Trauner DA. 1996. Visuomotor performance in children with infantile nephropathic cystinosis. Percept Mot Skills 82:67−75.

Trauner DA, Chase C, Scheller J, Katz B, Schneider JA. 1988. Neurological and cognitive deficits in children with cystinosis. J Pediatr 112(6):912−914.

Vogel DG, Malekzedah MH, Cornford ME, Schneider JA, Shields WD, Vinters HV. 1990. Central nervous system involvement in nephropathic cystinosis. J Neuropathol Exp Neurol 49:591−599.

Wechsler D. 2002. Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III). San Antonio, TX: Psychological Corporation.

Williams BLH, Schneider JA, Trauner DA. 1994. Global intellectual deficits in cystinosis. Am J Med Genet 49:83−87.