Title

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Journal

Pediatric Nephrology: Journal of the International Pediatric Nephrology Association, 25(10)

ISSN

1432-198X

Authors

Trauner, Doris A.
Williams, Jennifer
Ballantyne, Angela O.
et al.

Publication Date

2010-10-01

DOI

10.1007/s00467-010-1589-8

Peer reviewed

Pediatr Nephrol (2010) 25:2061–2066
DOI 10.1007/s00467-010-1589-8

ORIGINAL ARTICLE

Neurological impairment in nephropathic cystinosis: motor coordination deficits

Doris A. Trauner · Jennifer Williams · Angela O. Ballantyne · Amy M. Spilkin · Jennifer Crowhurst · John Hesselink

Received: 19 February 2010 / Revised: 20 May 2010 / Accepted: 2 June 2010 / Published online: 22 July 2010

Abstract Nephropathic cystinosis is a rare genetic metabolic disorder that results in accumulation of the amino acid cystine in lysosomes due to lack of a cystine-specific transporter protein. Cystine accumulates in cells throughout the body and causes progressive damage to multiple organs, including the brain. Neuromotor deficits have been qualitatively described in individuals with cystinosis. This study quantitatively examined fine-motor coordination in individuals with cystinosis. Brain magnetic resonance imaging (MRI) scans were also performed to determine whether structural changes were associated with motor deficits. Participants were 52 children and adolescents with infantile nephropathic cystinosis and 49 controls, ages 2–17 years, divided into preacademic and school-age groups. Results indicated that both the preacademic and school-age cystinosis groups performed significantly more poorly than their matched control groups on the Motor Coordination Test. Further, the level of performance was not significantly different between the preacademic and school-age groups. There were no significant differences in motor coordination scores based on MRI findings. This is the first study to document a persistent, nonprogressive, fine-motor coordination deficit in children and adolescents with cystinosis. The fact that these difficulties are present in the preschool years lends further support to the theory that cystinosis adversely affects neurological functioning early in development. The absence of a relationship between brain structural changes and motor function suggests that an alternative cause for motor dysfunction must be at work in this disorder.

Keywords Motor coordination · VMI · Cystinosis · Neurological impairment · Brain MRI · Cystine

D. A. Trauner · J. Williams · A. O. Ballantyne · A. M. Spilkin · J. Crowhurst
Department of Neurosciences, University of California, San Diego, School of Medicine, San Diego, CA, USA

D. A. Trauner
Department of Pediatrics, University of California, San Diego, School of Medicine, San Diego, CA, USA

J. Hesselink
Department of Radiology, University of California, San Diego, School of Medicine, San Diego, CA, USA

D. A. Trauner
Rady Children's Hospital San Diego, San Diego, CA, USA

D. A. Trauner (✉)
Department of Neurosciences, UCSD School of Medicine, 9500 Gilman Drive, MC 0935, La Jolla, CA 92093-0935, USA
e-mail: dtrauner@ucsd.edu

Introduction

Nephropathic cystinosis is a rare genetic metabolic disorder that results in accumulation of the amino acid cystine in lysosomes due to lack of a cystine-specific transporter protein [1–3]. The infantile form of the disorder is typically diagnosed with failure to thrive and renal dysfunction (Fanconi syndrome) in the first year of life [4]. Cystine accumulates in cells throughout the body and causes progressive damage to multiple organs,

including the brain. Neuropathological studies have shown cystine crystals within neural tissue [5, 6]. Central nervous system (CNS) involvement has been demonstrated in neuroimaging studies, which have documented cerebral atrophy and central volume loss [7–9]. Studies have linked brain structure and various aspects of cognition in individuals with cystinosis [10–12]. Most of those studies, however, took place before the advent of an effective treatment for the disease. Since the use of cysteamine has become the standard treatment for individuals with cystinosis, preservation of renal function is now possible for many years. Possible prevention of brain abnormalities must also be considered in light of current treatment.

Neuropsychological studies have shown that individuals with cystinosis have IQ and language within the normal range [13, 14] but specific nonverbal deficits [15, 16]. In particular, deficits are seen in the domains of visual spatial skills, visual–motor integration, visual memory, and processing speed, with a sparing of visual perception [15–19]. This specific pattern has been observed across the age range from preschool through adulthood [15, 16, 18], suggesting the possibility that the genetic disorder may exert a very early effect on brain development rather than the neurological effects being the result of a progressive decline in cognitive functioning as cystine continues to accumulate in the brain.

Neuromotor deficits in cystinosis were qualitatively described more than 20 years ago [7, 8, 20]. In this study, we greatly expand on the previous observations by examining fine-motor coordination in a large group of children and adolescents with cystinosis, all of whom have been treated with cysteamine since early life. We used the standardized Motor Coordination Test of the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI-5) [21] to obtain a quantitative assessment of motor coordination. Magnetic resonance imaging (MRI) scans were performed on all children and adolescents in the study with cystinosis so that structure–function analyses could be performed. We hypothesized that children and adolescents with cystinosis would exhibit fine-motor difficulties on the VMI-5 Motor Coordination Test. This study also examined fine-motor skills as a function of age group, which may shed light on the underlying pathophysiology of the disease.

Methods

Participants

Participants were 52 children and adolescents with infantile nephropathic cystinosis and 49 controls, ages 2–17 years. The cystinosis and control groups were divided into preacademic (ages 2–5 years) and school-age (ages 6–17 years) groups due to the many developmental and academic milestones that occur at the start of school (e.g. ability to hold a pencil to write) that might be expected to influence fine-motor performance. This testing was part of a larger, longitudinal study of brain structure and function in cystinosis. Each participant was diagnosed with infantile nephropathic cystinosis, as confirmed by clinical presentation and by assays documenting elevated leukocyte cystine concentrations. Individuals with cystinosis were excluded from the study if they were in renal failure, were on dialysis, were acutely ill, or had any other condition that might adversely affect cognitive function. Unfortunately, we were unable to acquire specific information about renal function on most of the patients because of variability in response from their treating physicians, variability in timing of blood and urine tests around the time of our testing, and differences in the types of tests performed by the treating physicians. However, some of these children participated in another study at the same time as ours, and all had estimated glomerular filtration rates (eGFRs) between 79 and 122 mL/min per 1.73 m^2 or stage 1 or 2 kidney disease [22]. At the time of testing, all cystinosis participants were on the standard prescribed medical regimen, which includes cysteamine, vitamin D, calcium and phosphate replacement, and thyroid hormone [23]. Cystinosis participants were recruited through the Cystinosis Foundation, the Cystinosis Research Network, and the Cystinosis Research Foundation. Participants in the control group were identified through advertisements placed in parent magazines and by fliers placed at various venues for children throughout the community (e.g. public libraries, YMCAs). The cystinosis and control participants were group-matched on the demographic variables of sex, chronological age, and socioeconomic status (SES) based on the Hollingshead Four Factor Index of Social Status [24]. All controls had normal developmental and medical histories. Informed consent for each participant was obtained according to the University of California, San Diego, Human Research Protection Program (HRPP) procedures, and the study was approved by the HRPP.

Measures

Fine-motor coordination

The Motor Coordination Test of the VMI-5 [21] was administered to all participants. The VMI-5 is normed for individuals between the ages of 2 years 0 months and 18 years 11 months and yields a standard score with a mean of 100 and standard deviation (SD) of 15. All

participants were presented with a series of geometric designs and required to draw each design within a double-lined path without going outside the lines. Items increased in difficulty throughout the test. Children younger than 5 years of age first demonstrated whether they were able to sit in a chair without help, hold a pencil with thumb and fingertips, and hold paper with one hand and draw with the other.

Intellectual ability

All cystinosis and control participants received an age-appropriate Wechsler Intelligence Scale [Wechsler Preschool and Primary Scale of Intelligence - III (WPPSI-III), Wechsler Intelligence Scale for Children - III (WISC-III), WISC-IV, or Wechsler Adult Intelligence Scale - III (WAIS-III)] [25–28]. Sixty-two participants received the WPPSI-III, 27 the WISC-III, ten the WISC-IV, and two the WAIS-III. Since the WISC-IV does not yield Verbal IQ (VIQ) or Performance IQ (PIQ) scores, the WISC-IV Verbal Comprehension Index (VCI) was substituted for VIQ and the WISC-IV Perceptual Reasoning Index (PRI) was substituted for PIQ.

Brain neuroimaging

Brain MRI scans were attempted on all participants with cystinosis. Scans were successfully completed on 46 children and adolescents. All scans were performed on a GE 1.5-Tessla unit at UCSD and were independently reviewed by a neuroradiologist (JH) who had no information on the participants' diagnoses. Scans were rated as normal, mild volume loss, and moderate to severe volume loss. Isolated Chiari type I malformations were also identified as a separate category.

White blood cell cystine levels

We were able to obtain results of white blood cell (WBC) cystine levels measured within 1 month of our testing from physicians caring for 29 participants. We were unable to acquire information about the methods used to measure cystine levels.

Statistical analyses

Potential group differences between the cystinosis and control groups within both the preacademic and school-age groups on the demographic variables of age at the time of testing, SES, sex, VIQ, and PIQ were analyzed using independent *t* tests and chi-square analyses, as appropriate. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) frameworks were used to analyze potential differences on the Motor Coordination Test between the cystinosis and control groups and between the preacademic and school-age groups. ANOVA was also used to determine whether brain structural differences were associated with motor coordination results. Lastly, the relationship between age and MRI findings was analyzed using a correlation analysis.

Results

Demographic variables

Table 1 lists group means, SDs, and significance values for the demographic variables. In the preacademic group, there were no significant differences between the cystinosis and control groups on Age at Testing, SES, or VIQ; however, PIQ was significantly lower in the cystinosis group compared with the control group (t=-2.491,

Table 1 Summary of demographic variables and significance values for the cystinosis and control groups

	Preacademic group			School-age group		
	n=50			n=51		
	Cystinosis n=26	Control n=24	p	Cystinosis n=26	Control n=25	p
Mean Age at Testing	4y 2m±9m	4y 4m±11m	NS	10y 8m±3y 7m	9y 9m±3y 3m	NS
Mean SES[a]	2.27±0.96	2.21±1.02	NS	1.92±0.84	1.84±0.90	NS
Sex	13 M; 13 F	14 M; 10 F	NS	18 M; 8 F	15 M ; 10 F	NS
VIQ	97.85±11.52	101.04±8.76	NS	92.23±13.39	102.96±7.99	0.001
PIQ	90.27±13.04	100.33±15.32	0.02	88.27±16.40	107.32±15.33	<0.001

[a] Based on the Hollingshead Four Factor Index of Social Status [23], with 1 being the highest and 5 being the lowest socioeconomic status

y years, *m* months, *M* male, *F* female, *SES* socioeconomic status, *VIQ* Verbal IQ, *PIQ* Performance IQ

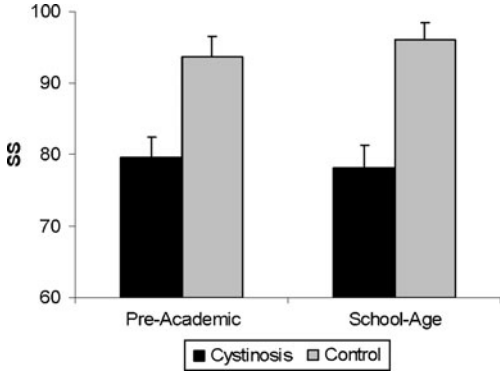

Fig. 1 Mean standard scores on the Motor Coordination Test for the cystinosis and control preacademic and school-age groups

p=0.016). In the school-age group, there were no significant differences between the cystinosis and control groups on Age at Testing or SES. Although still within normal limits, VIQ and PIQ were significantly lower in the cystinosis group than in the control group (t=-3.489, p=0.001; t=-4.281, $p\leq$0.001, respectively).

VIQ and PIQ were individually assessed as covariates for the analysis of motor coordination and were found to contribute a significant portion of variance to Motor Coordination Test scores. Nonetheless, when either VIQ or PIQ was partialled out, all significant differences between the cystinosis and control groups remained. Due to the fact that the analysis of Motor Coordination scores with IQ as a covariate is somewhat artificial (i.e. the child functions as a unitary whole), and significant differences remained even after covarying for either VIQ or PIQ, the results presented below represent performance without IQ as a covariate.

Fine-motor coordination

Fig. 1 presents Motor Coordination Test performance in preacademic and school-age cystinosis and control groups. ANOVA results indicated that the cystinosis group performed significantly more poorly than the control group on the Motor Coordination Test (F=32.01, p<0.001). Follow-up ANOVAs showed this pattern was significant within both the preacademic (F=12.39, p=0.001) and school-age (F=20.12, p<0.001) groups. ANOVA results showed the level of performance on the Motor Coordination Test was not significantly different between the preacademic and school-age groups. In addition, well over half of the cystinosis participants (approximately 60%) performed below normal limits (standard score<85) on the Motor Coordination Test, whereas one fifth (approximately 20%) of control participants scored below normal limits.

Table 2 Mean score (± standard deviation) on the Motor Coordination Test according to brain magnetic resonance imaging (MRI) findings in the cystinosis group

Normal MRI (n=25)	Mild volume loss (n=11)	Moderate to severe volume loss (n=5)	Isolated Chiari I malformation (n=5)
77.8±13.7	87.8 ±15.6	75.6±12.5	76.2±11.5

There were no significant differences between the Normal MRI group and any of the three abnormal MRI subgroups

Brain neuroimaging

Of the 46 useable MRI scans performed on cystinosis participants, 25 were read as normal, 11 had mild volume loss, five had moderate to severe volume loss, and five had an isolated Chiari I malformation (see Fig. 2 for control and cystinosis participant MRI examples). No significant differences were detected in motor coordination scores based on MRI findings (see Table 2). Although the group with mild volume loss achieved a higher score

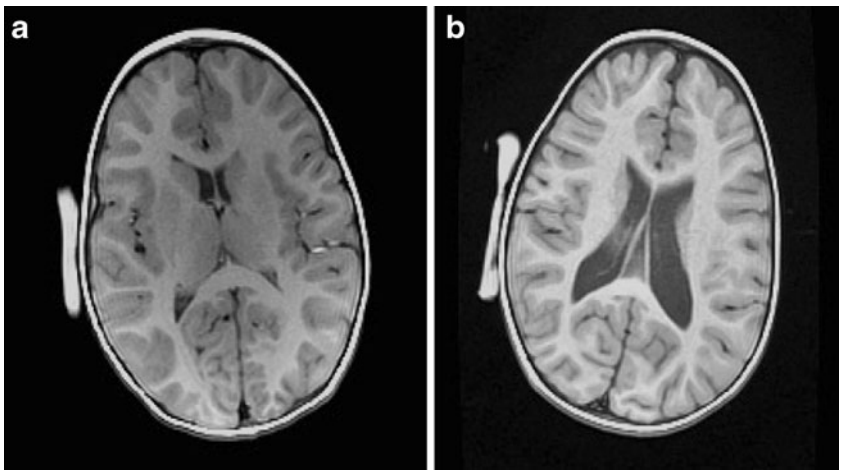

Fig. 2 **a** Brain magnetic resonance image (MRI) of 4-year-old typically developing control. **b** Brain MRI of a 5-year-old child with cystinosis, demonstrating mild central volume loss with ventriculomegaly

on motor coordination than did the group with normal scans, this difference was not statistically significant. In addition, the groups with moderate to severe volume loss or an isolated Chiari I malformation demonstrated no differences in performance when compared with the group with normal scans. It should be noted, however, that there were small numbers of children in the abnormal scan subgroups. Furthermore, there were no age-related differences in MRI findings. Specifically, there was no correlation between age at scanning and presence or absence of brain-volume loss.

We did not record the dose of cysteamine that each child was taking at the time of testing. However, leukocyte cystine levels drawn within 1 month of psychometric testing were available for 29 cystinosis patients. Twenty-one of these 29 had values of 1.0 nmol half cystine per milligram of protein, the current therapeutic goal for treatment of cystinosis [29]. All but two of the 29 samples had cystine levels <2 nmol half cystine per milligram of protein, a level thought to be adequate to diminish the rate of decline in renal function [30]. There was no difference in motor coordination scores for the two children whose cystine levels were >2 compared with those whose levels were <2, although no statistical analyses could be performed due to the small number of children with high cystine levels.

Discussion

This is the first study to document a persistent, nonprogressive, fine-motor-coordination deficit in cystinosis individuals using a quantitative standardized assessment tool. Mean scores on the Motor Coordination Test in both the preacademic and school-age cystinosis groups were below normal compared with age-referenced norms (mean scores 79.58 and 78.08, respectively) and were significantly lower than matched control groups. Of note, this fine-motor coordination deficit is not due to the influence of cognitive ability (either VIQ or PIQ) and thus represents a unique neuromotor component of the disease. Furthermore, this is the first study to document that brain MRI findings do not explain the motor coordination deficits in a group of cystinosis individuals, all of whom received early treatment with cysteamine.

Importantly, our results show that the fine-motor coordination deficit in cystinosis is present from the preschool years and persists throughout adolescence. They also demonstrate that brain structural changes do not account for the observed motor coordination deficits. The fact that both structural and functional changes are present in the preschool years lends further support to the theory that cystinosis adversely affects the brain early in development [16, 18]. Possible causes of this early negative impact on brain structure and function include an adverse effect of very early cystine accumulation in the brain (possibly in utero) prior to the introduction of treatment with cysteamine, or a direct effect of the gene on brain development. It is also possible that treatment with cysteamine could be responsible for motor coordination problems; however, earlier reports of fine-motor deficits in cystinosis individuals [20] included individuals who had never received cysteamine, making it less likely that treatment of the underlying disease is responsible for the neuromotor abnormalities. Finally, it is possible that cysteamine is improving neurological function and that the children might have more severe deficits had they not been on this treatment. Further studies will be required to clarify this question.

The finding of significant motor coordination deficits in children with cystinosis has important implications for intervention. Early recognition and treatment of such problems may lead to improved life skills, such as self-care (buttoning, using scissors, manipulating utensils), writing, drawing, eye–hand coordination, and academic and vocational ability, potentially leading to improved quality of life.

Acknowledgments This research was supported by NINDS grant # NS043135 (D.A. Trauner, P.I.). We thank the National Cystinosis Foundation, the Cystinosis Research Network, the Cystinosis Research Foundation, and the parents and children who participated in the study.

References

1. McDowell G, Isogai T, Tanigami A, Hazelwood S, Ledbetter D, Polymeropoulos MH, Lichter-Konecki U, Konecki D, Town MM, Van't Hoff W, Weissenbach J, Gahl WA (1996) Fine mapping of the cystinosis gene using an integrated genetic and physical map of a region within human chromosome band 17p13. Biochem Mol Med 58:135–141
2. Peters U, Senger G, Rahlmann M, DuChesne I, Stec I, Kohler MR, Weissenbach J, Leal SM, Koch HG, Deufel T, Harms E (1997) Nephropathic cystinosis (CTNS-LSB): Construction of a YAC contig comprising the refined critical region on chromosome 17p13. Eur J Hum Genet 5:9–14
3. Town M, Jean G, Cherqui S, Attard M, Forestier L, Whitmore SA, Callen DS, Gribouval O, Broyer M, Bates GP, van't Hoff W, Antignac C (1998) A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. Nat Genet 18:319–324
4. Gahl WA, Thoene JG, Schneider JA (2001) Cystinosis: a disorder of lysosomal membrane transport. In: Scriver CR,

Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited diseases. McGraw-Hill, New York, pp 5085–5108
5. 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
6. Levine S, Paparo G (1982) Brain lesions in a case of cystinosis. Acta Neuropathol 57:217–220
7. Cochat P, Drachman R, Gagnadoux M-F, Pariente D, Broyer M (1986) Cerebral atrophy and nephropathic cystinosis. Arch Dis Child 61:401–403
8. Ross DL, Strife F, Towbin R, Bove KE (1982) Nonabsorptive hydrocephalus associated with nephropathic cystinosis. Neurology 32:1330–1334
9. 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
10. 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
11. Nichols S, Press GA, Schneider JA, Trauner DA (1990) Cortical atrophy and cognitive performance in infantile nephropathic cystinosis. Pediatr Neurol 6:379–381
12. Bava S, Theilmann RJ, Sach M, May SJ, Frank LR, Hesselink JR, Vu D, Trauner DA (2010) Developmental changes in cerebral white matter microstructure in a disorder of lysosomal storage. Cortex 46:206–216
13. Ballantyne AO, Scarvie KM, Trauner DA (1997) Academic achievement in individuals with infantile nephropathic cystinosis. Am J Med Genet 74:157–161
14. Williams B, Schneider JA, Trauner DA (1994) Global intellectual deficits in cystinosis. Am J Med Genet 49:83–87
15. Ballantyne AO, Trauner DA (2000) Neurobehavioral consequences of a genetic metabolic disorder: Visual processing in infantile nephropathic cystinosis. Neuropsychiatr Neuropsychol Behav Neurol 13:254–263
16. Spilkin AM, Ballantyne AO, Babchuck LR, Trauner DA (2007) Non-verbal deficits in young children with a genetic metabolic disorder: WPPSI-III performance in cystinosis. Am J Med Genet B Neuropsychiatr Genet 144B:444–447
17. Scarvie KM, Ballantyne AO, Trauner DA (1996) Visuomotor performance in children with infantile nephropathic cystinosis. Percept Mot Skills 82:67–75
18. Trauner DA, Spilkin AM, Williams J, Babchuck L (2007) Specific cognitive deficits in young children with cystinosis: Evidence for an early effect of the cystinosin gene on neural function. J Pediatr 151:192–196
19. Spilkin AM, Ballantyne AO, Trauner DA (2009) Visual and verbal learning in a genetic metabolic disorder. Neuropsychologia 47:1883–1892
20. Trauner DA, Chase C, Scheller J, Katz B, Schneider JA (1988) Neurological and cognitive deficits in children with cystinosis. J Pediatr 112:912–914
21. Beery KE, Beery NA (2004) The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) - 5th Edition. NCS Pearson, Minneapolis, MN
22. Dohil R, Ganfioti JA, Cabrera BL, Fidler M, Schneider JA, Barshop BA (2010) Long-term treatment of cystinosis in children with twice-daily cysteamine. J Pediatr 156:823–827
23. Adamson MD, Anderson HC, Gahl WA (1989) Cystinosis. Semin Nephrol 9:147–161
24. Hollingshead AB (1975) Four Factor Index of Social Status. Yale University Department of Sociology, New Haven
25. Wechsler D (1997) Wechsler Adult Iintelligence Scale - III (WAIS-III). Psychological Corporation, San Antonio
26. Wechsler D (1991) Wechsler Intelligence Scale for Children - III (WISC-III). Psychological Corporation, San Antonio
27. Wechsler D (2002) Wechsler Preschool and Primary Scale of Intelligence - 3rd edn (WPPSI-III). Psychological Corporation, San Antonio
28. Wechsler D (2003) Wechsler Intelligence Scale for Children - 4th edn (WISC-IV). Psychological Corporation, San Antonio
29. Gahl WA, Thoene JG, Schneider JA (2002) Cystinosis. N Engl J Med 347:111–121
30. Markello TC, Bernardini IM, Gahl WA (1993) Improved renal function in children with cystinosis treated with cysteamine. N Engl J Med 328:1157–1162