ORIGINAL ARTICLE

Neurocognitive functioning in school-aged cystinosis patients

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Abstract

Introduction Cystinosis is an autosomal recessive disorder leading to intralysosomal cystine accumulation in various tissues. It causes renal Fanconi syndrome and end stage renal failure around the age of 10 years if not treated with cysteamine. Children with cystinosis seem to have a normal intelligence but frequently show learning difficulties. These problems may be due to specific neurocognitive deficits rather than impaired renal function. Whether cysteamine treatment can improve cognitive functioning of cystinosis patients is thus far unknown. We aim to analyze neurocognitive functioning of school-aged cystinosis patients treated with cysteamine in order to identify specific deficits that can lead to learning difficulties.

Patients and methods Fourteen Dutch and Belgian school-aged cystinosis patients were included. Glomerular filtration rate was estimated using the Schwartz formula. Children were tested for general intelligence, visual-motor integration, inhibition, interference, sustained attention, accuracy, planning, visual memory, processing speed, motor planning, fluency and speed, and behavioural and emotional functioning using standardized methods.

Results Glomerular filtration rate ranged from 22 to 120 ml min^{-1} 1.73 m^{-2}. Median full-scale intelligence was below the average of a normal population (87, range 60–132), with a discrepancy between verbal (median 95, range 60–125) and performance (median 87, range 65–130) intelligence. Over 50% of the patients scored poorly on visual-motor integration, sustained attention, visual memory, planning, or motor speed. The other tested areas showed no differences between patients' and normal values.

Conclusion Neurocognitive diagnostics are indicated in cystinosis patients. Early recognition of specific deficits and supervision from special education services might reduce learning difficulties and improve school careers.

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Abbreviations

GFR	Glomerular filtration rate
IQ	Intelligence quotient
VMI	Visual motor integration
CBCL	Child behavior checklist

Introduction

Cystinosis is a rare autosomal recessive disorder caused by mutations in the *CTNS* gene, encoding the lysosomal cystine carrier cystinosin. This results in intralysosomal accumulation of the amino acid cystine (Town et al. 1998). The most frequent and severe infantile form has an incidence of 1 case in every 100,000 to 200,000 live births. Children present with renal Fanconi syndrome, mostly during the first year of life. This generalized proximal tubular damage progresses towards end stage renal disease around the age of 10 years. Extra-renal organs are also affected, including eyes, endocrine organs, muscles, and central nervous system. Cystinosis is treated by administration of the cystine-depleting agent cysteamine, which slows down the progression of renal failure and protects extra-renal organs (Gahl et al. 2002).

Previously it was believed that since children with cystinosis have a normal intelligence, no learning difficulties should be expected. Moreover, poor school results were often explained by renal disease or seen as a consequence of a chronic illness and its treatment. In 1988, however, it was demonstrated that cystinosis patients have neurocognitive impairments that cannot be attributed to their decreased renal function (Trauner et al. 1988). Despite a normal intelligence, deficits in visual information processing and tactile recognition processing have been reported. As a result, poor school performances, in particular for spelling and arithmetic, have been found (Ballantyne et al. 1997; Colah and Trauner 1997; Spilkin et al. 2007; Williams et al. 1994; Wolff et al. 1982).

The aim of this study was to analyze neurocognitive functioning in Dutch and Belgian school-aged cystinosis patients treated with cysteamine starting from an early age in order to identify specific deficits that might lead to learning difficulties and to evaluate the influence of cysteamine treatment. Furthermore, we analyzed the effect of different *CTNS* mutations on neurocognitive functioning.

Patients and methods

Fourteen school-aged cystinosis patients (age 6–17 years), treated in three Dutch and two Belgian hospitals, were included. Cystinosis was diagnosed at a mean age of 1 year and 10 months, and cysteamine treatment was started immediately thereafter and monitored by measuring white blood cell (WBC) cystine levels every 2–4 months. The diagnosis was confirmed by mutational analysis of the *CTNS* gene in 13/14 patients. "Whole life" mean WBC cystine levels were calculated from all measurements after the onset of cysteamine treatment. The glomerular filtration rate (GFR) at the moment of testing was estimated using the Schwartz formula (Schwartz et al. 2009). Patients were scheduled for neurocognitive assessment after written informed consent was obtained from parent(s) and patients ≥12 years of age. A standard test battery was completed by all patients. These tests were administered by a trained psychology assistant, who was supervised by a research psychologist. The study was approved by the institutional review board of the Radboud University Medical Centre.

General intelligence

WISC-III

The Wechsler Intelligence Scale for Children, 3rd edition (WISC-III) is a standardized method to test the intelligence quotient (IQ) in children 6–16 years of age (Kort et al. 2002; Wechsler 1991). Patient 8 (17.4 years of age) completed the Wechsler Adult Intelligence Scale (WAIS). Three general measures were derived: full-scale IQ, verbal IQ, and performance IQ.

Neurocognitive function

VMI

The Developmental Test of Visual-Motor Integration (VMI) measures visual-motor integration skills, indicated by the ability to copy increasingly complex geometric forms (Beery 1997).

Stroop Color-Word Interference Test

The Stroop Color-Word Interference Test measures inhibition and interference (e.g., the ability to suppress a habitual response in support of an unusual one) (Hammes 1978). It is divided into word reading (reading color names printed in black) and color naming (naming the print colors of colored bars and naming the print colors of color names when both are not the same). The latter measures the ability to say the print color while suppressing the response to say the color name, which is an interference test. Although this test was originally developed for adults, standardized age norms (7–12 years) for the Dutch population were available and used. The test was not performed in patient 2, since she was <7 years of age and in patients 4 and 8, since they were >12 years of age.

Bourdon-Vos Test

The Bourdon-Vos Test measures sustained attention and accuracy (Vos 1998). Children had to cross out all groups of four dots on a page filled with groups of three, four, and

five dots. Scores for both speed and accuracy were normed and evaluated. Patient 13 was too tired to complete the test.

Rey-Osterrieth Complex Figure

Rey's figure was administered to measure planning (organization) and visual memory (Bernstein and Waber 1996). Children had to copy a complex figure and draw it from memory immediately thereafter (immediate recall) and after a delay of 20 min (delayed recall). Since the test has a norm only for children up to 14 years of age, it was not performed in patients 4 and 8.

Computerized drawing task

A computerized drawing task was administered to evaluate processing speed, motor planning, motor fluency, and motor speed (Schoemaker et al. 1994). Drawing movements were digitally recorded by a digitizing tablet and a wireless electronic pen. Processing speed was indicated by mean reaction time, motor planning by mean duration of pauses between small and large elements, motor fluency by mean number of velocity peaks, and motor speed by mean drawing speed (cm/s).

Behavioral and emotional functioning

CBCL

The Child Behavior Checklist (CBCL) is used to recognize problems of behavioral and emotional functioning (Achenbach 1991). Three parallel versions of the Dutch CBCL were administered: a parent's version, a patient's version for children ≥12 years of age, and a teacher's version (Verhulst et al. 1996, 1997a, b). Scores indicating internalizing, externalizing, and total problems were derived.

Statistical analysis

Correlations between full-scale, verbal, and performance IQ and GFR and between full-scale, verbal, and performance IQ and "whole life" WBC cystine levels were estimated using the Spearman rank correlation method. The general intelligence measures of patients having a homozygous 57 kb deletion of the CTNS gene were compared with those of patients with other mutations using the Mann-Whitney U tests. Values were considered statistically significant at $P < 0.05$.

Results

Data on GFR, WBC cystine levels, CTNS gene mutations, and educational levels of the parents are shown in Table 1.

Eight patients were homozygous for the large 57 kb deletion in the CTNS gene, and five patients were heterozygous and had the 57 kb deletion combined with another mutation; DNA analysis was not performed in patient 13. GFR ranged from 22 to 120 (normal ≥90) ml min^{-1} 1.73 m^{-2}, seven patients had a decreased GFR of <90 ml min^{-1} 1.73 m^{-2}, and patient 4 had a functioning renal graft. Mean WBC cystine levels were within the range of healthy carriers (0.26–0.86 nmol half-cystine/mg protein) in 5/14 patients, indicating adequate cysteamine treatment (Table 1). Results of the neurocognitive tests are shown in Table 2. Scores were defined as average, poor, or low according to the instructions in the test manuals. In all tests except for Rey's figure, a score of 1 standard deviation (SD) or more above or below the average was considered to be significant. In Rey's figure, scores were qualified as poor if below or equal to the 10th percentile and good if above or equal to the 90th percentile. The WISC-III, WAIS, and VMI have an average score of 100, with an SD of 15.

General intelligence

Median full-scale IQ was 87 (range 60–132), median verbal IQ 87 (range 60–125), and median performance IQ 95 (range 65–130). Five patients (36%) scored ≥1 SD below the average for full-scale IQ. In five patients (36%), the verbal IQ was ≥1 SD higher than the performance IQ, none of the patients had a significantly better performance IQ compared to the verbal IQ.

Neurocognitive functions

All 14 children completed the VMI. Seven children (50%) had a poor performance (≤85 points), and none had a good performance (≥115 points) on this test.

The Stroop Color-Word Interference Test was performed in 11/14 patients and showed no abnormalities: 5 children (45%) had an average performance, 3 children (27%) had a poor performance, and 3 children (27%) had a good performance.

The Bourdon-Vos Test was performed in 13/14 patients. Only four patients (31%) showed a normal sustained attention, while the other nine patients (69%) showed a delayed sustained attention. There were no evident problems in accuracy: six children (46%) had a good performance, five children (38%) had a poor performance.

The Rey-Osterrieth Complex Figure was completed by 12/14 children. Four patients (33%) had a score of poor on planning (organization), only one patient (8%) had a score of good on planning items. Three patients (25%) had a score of poor on visual memory, none had a score of good on this item.

The computerized drawing task was completed by all 14 children. Two patients (14%) had a good score on processing speed, and four patients (29%) had a poor score

Table 1 Clinical data on the patients and educational levels of the parents

Patient	Age (years)	Sex	Age at onset of cysteamine therapy (years)	DNA analysis of CTNS gene	Renal status	GFR (ml min^{-1} 1.73m^{-2})	Mean (SD) cystine levels[a] (nmol half-cystine/mg protein)	Educational background father	Educational background mother
01	10.0	F	1.2	hom 57 kb del	NK	22	0.98 (0.46)	U	U
02	6.3	F	1.3	57 kb del/c.del18 _21GACT	NK	86	3.10 (1.36)	V	V
03	11.1	F	1.10	hom 57 kb del	NK	48	0.74 (0.64)	V	LS
04	15.5	F	1.8	hom 57 kb del	Tx	72	0.92 (0.52)	HV	HV
05	10.7	M	9.0	57 kb del/c.198 _218del21	NK	113	1.10 (0.36)	V	HS
06	8.4	M	1.3	hom 57 kb del	NK	84	0.86 (0.54)	V	HS
07	9.2	M	0.9	hom 57 kb del	NK	100	0.96 (0.52)	V	LS
08	17.4	M	0.6	hom 57 kb del	NK	57	0.84 (0.40)	HV	V
09	11.8	F	1.4	57 kb del/c.665 A>G	NK	120	0.64 (0.34)	V	V
10	11.8	F	1.4	57 kb del/c.665 A>G	NK	120	0.60 (0.34)	V	V
11	11.3	M	2.8	57 kb del/c.926dup	NK	89	2.03 (1.28)	V	HV
12	7.4	M	0.10	hom 57 kb del	NK	112	4.75 (2.62)	U	U
13	8.1	M	1.6	Not done	NK	118	1.56 (0.68)	V	LS
14	8.6	M	0.10	hom 57 kb del	NK	103	0.96 (0.74)	LV	LS

NK Native kidney, *Tx* renal transplantation, *V* vocational education, *LV* lower vocational education, *HV* higher vocational education, *LS* lower secondary education, *HS* higher secondary education, *U* university education

[a] Normal values for healthy carriers: 0.26–0.86 nmol half-cystine/mg protein

on this item. One patient (7%) had a good score on motor planning, whereas eight patients (57%) had a poor score on this measure. Motor fluency and motor speed showed no evident problems: three patients (21%) showed a good score and two patients (14%) showed a poor score on motor fluency, while two patients (14%) showed a good score and three patients (21%) showed a poor score on motor speed.

Behavioral and emotional functioning

Teachers reported poor school performances in two or more areas in seven patients (50%, data not shown). The reported problem areas included arithmetic, spelling, reading comprehension, and knowledge of the world. All seven of these patients (patients 01, 03, 07, 08, 09, 10, and 14) had a risk profile for neurocognitive dysfunction, e.g., they showed a low general intelligence level or a discrepancy between verbal and performance IQ and/or a poor performance on neurocognitive tasks. No significant behavioral or emotional problems were reported by parents or patients.

Statistical analysis

We found no significant correlation between full-scale, verbal, and performance IQ and GFR. Unexpectedly, a significant positive correlation was found between mean "whole-life" WBC cystine levels and full-scale IQ ($R=0.68$, $P=0.007$),

verbal IQ ($R=0.57$, $P=0.033$), and performance IQ ($R=0.73$, $P=0.003$). Full-scale, verbal, and performance IQ were not different between patients having the homozygous 57 kb deletion and patients with other mutations.

Discussion

This study aimed at examining neurocognitive functioning in school-aged cystinosis patients treated with cysteamine starting at an early age in order to find evidence for clinically observed learning difficulties in this patient group. We found a poorer performance on visual-motor integration (VMI), sustained attention (Bourdon-Vos Test), visual memory (Rey's figure), planning (Rey's figure, drawing task), and motor speed (drawing task). The finding of a full-scale IQ just below the average with a relative good verbal IQ and poor performance IQ combined with poor executive functions is in line with the results of other international studies on neurocognitive functioning in children with cystinosis (Ballantyne et al. 1997; Colah and Trauner 1997; Spilkin et al. 2007, 2009; Ulmer et al. 2009; Williams et al. 1994; Wolff et al. 1982).

Interestingly, teachers reported more school problems than parents and patients ≥12 years (CBCL). It should be noted however that scores on the CBCL are slightly distorted in pediatric populations (Perrin et al. 1991). This

Table 2 Test results

| Patient | WISC/WAIS | | | VMI | Stroop[a] | Bourdon[a] | | Rey's figure[a] | | Experimental drawing task[a] | | | |
	VIQ	PIQ	FIQ			Sustained attention	Accuracy	Planning	Visual memory	Processing speed	Motor planning	Motor fluency	Motor speed
01	96	75	84	87	=	−	=	=	=	=	+	=	=
02	125	130	132	94	ND[b]	=	+	=	=	−	−	=	=
03	111	88	100	73	+	−	+	+	=	=	−	=	−
04	117	101	111	97	ND[c]	=	+	ND[c]	ND[c]	=	=	=	=
05	86	94	88	110	=	=	−	=	=	=	−	+	=
06	79	80	77	83	=	=	=	−	−	=	=	=	=
07	96	78	86	94	+	−	−	=	=	=	−	=	=
08	81[d]	75[d]	77[d]	77	ND[c]	−	+	ND[c]	ND[c]	=	=	+	=
09	60	65	60	81	=	−	+	−	=	=	−	=	−
10	64	72	65	74	+	−	−	−	−	+	−	=	=
11	105	95	100	90	=	−	−	−	−	+	=	=	+
12	110	95	103	93	−	ND[e]	ND[e]	=	=	−	=	+	+
13	94	105	99	84	−	−	−	=	=	−	−	−	=
14	90	85	86	65	−	−	+	=	−	−	−	−	−

VIQ Verbal intelligence quotient, *PIQ* performance intelligence quotient, *FIQ* full-scale intelligence quotient, *VMI* visual-motor integration, *ND* not determined

[a] Cognitive function test results: = average performance (<1 SD below or above average, Rey's figure 10th-90th percentile), + good performance (≥1 SD above average, Rey's figure ≥90th percentile), − poor performance (≥1 SD below average, Rey's figure ≤10th percentile)

[b] Test not performed because patient was below 7 years of age

[c] Test not performed because patient was over 12 years of age (Stroop), over 14 years of age (Rey's figure)

[d] Tested with Wechsler Adult Intelligence Scale (WAIS)

[e] Test not performed because patient was too tired

is due to the fact that children suffering from a somatic disorder show an increased risk for overall adjustment problems, internalizing and (to a lesser extent) externalizing symptoms. Therefore, they are more likely to show higher scores on the scales of somatic complaints and internalizing problems when compared to their healthy peers (Lavigne and Faier-Routman 1992). It is known that patients over 12 years of age do not seem to recognize their emotional and learning difficulties (Delgado et al. 2005; Gipson et al. 2004), and it might be suggested that parents do not expect their children to have major school problems, since they seem to have a normal intelligence and in particular normal or even above normal verbal levels. A study using the CBCL conducted in 2005 on behavioral problems in children with cystinosis revealed more social problems in cystinosis patients compared to patients with another chronic disease (cystic fibrosis) and compared to healthy control subjects. However, in that study only the patients and their parents, and not the teachers, completed the checklists (Delgado et al. 2005). In our study, such behavioral problems were not reported.

A limitation of this study is the small study population, since cystinosis is a very rare disorder. We also found a broad heterogeneity in terms of general intelligence. On the other hand, the strength of this work lays in the broad pallet of standardized tests, which were adequately administered by a trained team of psychologists.

Pathogenesis of neurocognitive disturbances in cystinosis

The pathogenesis of brain involvement in cystinosis remains unclear. Thus far, three hypotheses have been postulated. These include progressive accumulation of cystine in brain cells (in particular oligodendrocytes), progressive development of intracranial microvascular disease, and alterations of the blood-brain barrier leading to cystine deposits within cerebral pericytes, thus making them unable to prevent circulating toxins from entering the central nervous system (Vogel et al. 1990).

A study performed on $ctns^{-/-}$ knockout mice showed spatial short-term memory impairments, comparable to the cognitive anomalies found in cystinosis patients. The highest cystine levels were found in the hippocampus, cerebellum, and brainstem, respectively (Maurice et al. 2009). In human cystinosis patients, cystine accumulates in all parts of the brain, especially in the basal ganglia (Jonas et al. 1987). Whether cysteamine therapy is able to influence learning difficulties remains unclear. Our study failed to demonstrate a positive effect of cysteamine therapy, evaluated by "whole-life" WBC cystine levels, on neurocognitive functioning. In line with our results, it should be noted that the study by Wolff et al. conducted on patients not treated with cysteamine showed a similar pattern of normal general

intelligence with relatively poor scores for performance IQ and relative good scores for verbal IQ (Wolff et al. 1982).

Interestingly, we found a positive correlation between WBC cystine levels and full-scale, verbal, and performance IQ results. This unexpected observation might be due to unknown side effects of cysteamine on brain function. Cysteamine is suggested to cross the blood-brain barrier as mixed disulfide with cysteine and is reduced in cerebro to free cysteamine. The administration of supraclinical doses of cysteamine (250 mg/kg) to rats showed a remarkable increase in cerebral and cerebellar levels of methionine, and a drop in cerebral levels of cysteine and an anti-oxidant compound, S-(2-aminoethyl)-L-cysteine ketimine decarboxylated dimer (AECK-DD), probably due to the oxidative effect of cysteamine (Pinto et al. 2009). It cannot be ruled out that the administration of high cysteamine doses might have a detrimental effect on the brain. Studies of cysteamine metabolites in the spinal fluid of cystinosis patients might help to clarify pathways involved in cerebral cysteamine metabolism in humans and to identify eventual markers of cysteamine-induced damage. Unfortunately, we could not determine "whole-life" cysteamine dose in our patients because it was not always correctly noted in the patient's records, and we had no information about compliance. In an earlier study, a negative association was found between the variance in cystine levels and performance IQ (Bava et al. 2010); these findings should be further examined in larger patient populations and in $ctns^{-/-}$ mice treated with cysteamine.

In our study, patients with the homozygous 57 kb deletion had a general intelligence comparable to those with heterozygous mutations. This suggests that the absence of the *CARKL* gene, which is another gene removed in patients with homozygous 57 kb deletion (Wamelink et al. 2008), does not contribute to the cerebral dysfunction of cystinosis patients.

Conclusion

Neurocognitive diagnostics aimed at visual-motor integration, visual memory, planning, sustained attention, and motor speed are indicated in all cystinosis patients from the age of 7–8 years. Deficits in these fields can lead to learning difficulties in reading, spelling, and arithmetic. For instance, poor visual motor integration, motor speed, and sustained attention may prevent the child from recognizing letter forms, recalling and writing them, and from meeting the time constraints often involved in school assignments. Early neuropsychological diagnostics can contribute to early recognition from special education services, which might reduce the development of these learning problems and result into targeted remedial teaching. Parents and teachers should be informed that possible deficits or "minor symptoms" might not be attributed to the general effects of

having a chronic disease. Further research on the etiology of specific deficits of neurocognitive functioning in school-aged cystinosis patients is recommended.

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