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Cognitive functions and behavioural profiles in children with cystinosis treated with cysteamine and correlation with treatment duration

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Abstract

Background: Cystinosis is a rare autosomal recessive disease. Children with nephropathic cystinosis (NCTN) have evidence of intellectual dysfunction and behavioural abnormalities which are attributed to renal dysfunction, metabolic disarrangement, and gene mutation. This study aimed to characterize the cognitive functions and behavioural profiles in nephropathic cystinosis patients on cysteamine therapy, and determine its relation to cysteamine treatment duration. In this analytical cohort study, 20 children with nephropathic cystinosis aged 6 years or above were compared to 26 children with chronic kidney disease (CKD) matched in age, sex, and CKD stage. All patients were subjected to full clinical and psychometric assessment using the Child Behaviour Checklist (CBCL) and the Arabic language version of Stanford-Binet test (SB).

Results: There was no significant difference between both groups regarding Stanford-Binet test (SB) and Child Behavioural Checklist (CBCL), apart from delinquent behaviour. Duration of cysteamine treatment was inversely correlated with short-term memory, thought, and sex problems.

Conclusions: Children with cystinosis have a wide range of neurocognitive and behavioural problems that still present after cysteamine treatment and may be related to impact of genetic mutation on brain structure and function. Longer duration of cysteamine treatment could have beneficial effects on some behavioural problems.

Keywords: Cognitive functions, Behavioural profiles, Cystinosis, Cysteamine

Background

Cystinosis is an autosomal recessive disease that leads to accumulation of cystine crystals in the body cells. Cystinosis can affect any organ in the body, especially the kidneys and eyes. The types of cystinosis depend on the age of onset of symptoms. The most common type is the infantile form. Initial symptoms include vomiting, dehydration, lack of feeding, and growth failure. If left untreated, cystinosis leads to renal and eye damage. Cystinosis is due to homozygous mutation in *CTNS* gene (cystinosin, lysosomal cystine transporter) which codes for protein transporter that transfers cysteine out of lysosomes. It can be diagnosed by slit-lamp examination, measurement of cysteine level in white blood cells, and or genetic mutation analysis [1–4].

Cysteine depleting therapy (cysteamine) can delay or prevent disease symptoms. The earlier the therapy begins, the better the results. If left untreated, cystinosis will result in renal failure by adolescence [3, 5, 6].

Cognitive disorders and behavioural disturbance have been reported in children with nephropathic cystinosis in previous studies; however, the cause of these disorders is

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not yet known [7, 8]. Cystinosis is associated with multiple neurological complications as structural brain abnormalities, impairment of cognitive functions, and learning disabilities [9]. Long-term studies showed that when cysteamine is given early, it may prevent neurocognitive complications [10–12]. Other studies found that neurocognitive and neurobehavioural profiles could be due to an early influence of the genetic mutation on brain function and structure [13].

In this study, we aimed to characterize neurobehavioural and neurocognitive changes in paediatric nephropathic cystinosis cases and find their temporal relation to cysteamine treatment.

Methods

Study design and setting

It was an analytical cohort study that was conducted at the Cystinosis Clinic, Center of Paediatric Nephrology and Transplantation (CPNT), Cairo University, Egypt, during the study period (from September 2020 to April 2021).

Participants

Twenty paediatric patients with confirmed nephropathic (NCTN) cystinosis and on regular cysteamine therapy were recruited. Patients with neurodevelopmental problem or uncontrolled hypothyroidism were excluded from the study. We also excluded children below the age of 6 years who were not able to perform psychometric assessment and any case with NCTN who were on cysteamine therapy for less than 1-year duration.

Twenty-six, age, sex, and CKD stage-matched patients with chronic kidney disease (CKD) were recruited from CKD follow-up clinic. Verbal and written informed consents were taken from the patients' guardians. This study was approved by the Research Ethics Committee, Kasr Alainy, Faculty of Medicine, Cairo University, and adhered to the Helsinki Declarations of biomedical ethics.

Sample size

Sample size calculation was carried out using G*Power 3 software [14]. A calculated minimum sample of 40 participants 1:1 distribution (20 patients with nephropathy cystinosis and 20 age- and sex-matched CKD cases) was needed to detect an effect size of 0.9 [15] in the mean neurocognitive functions and behavioural profiles scale scores (SB and CBCL test), with an error probability of 0.05 and 80% power on a two-tailed test.

Measures

Case notes were reviewed for relevant data retrieval (onset of the disease, clinical presentation, adherence to treatment, and laboratory data as complete blood count, serum electrolytes, blood gases, and thyroid profile). All patients enrolled in this study were subjected to full clinical assessment particularly anthropometric and blood pressure measurements. Psychometric assessment was done by using the Stanford Binet (SB) test and the Child Behaviour Checklist (CBCL) questionnaire.

Stanford-Binet (SB) test [16], Arabic version [17]: It is an examination to measure intelligence through scale scores for verbal, visual, and quantitative reasoning, and short-term memory).

Child behaviour checklist (CBCL) [18] questionnaire, Arabic version [19]: It is a parent report form to detect emotional, social, and behavioural problems. CBCL is used for children 6–18 years of age and includes different categories: anxious/depressed, withdrawn, somatic complaints, social problems, attention problems, thought problems, rule-breaking behaviour, and aggressive behaviour. Percentile scores below the 95th percentile (approximate *t*-score of 65 and below) are considered to be in the normal range. Percentile scores between the 95th and the 98th percentile (approximate *t*-scores of 65 to 70) are considered to be in the borderline range.

Statistical analysis

Data were verified, coded, and analysed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA) [20]. Descriptive statistics including means, standard deviations, medians, ranges, frequency, and percentages were calculated. Chi-square test was used to compare the difference in distribution of frequencies among different groups. For continuous variables, independent sample *t*-test was carried out to compare the means between groups. Multivariable logistic regression analysis was calculated to investigate the independent significant correlates of cystinosis (odds ratio (OR), 95% confidence interval (95% CI)). Predictors with proven statistical significance from the bivariate analyses were further included in the multivariable logistic regression models. p-value < 0.05 was considered significant.

Ethical consideration

This study was approved by the Research Ethics Committee, Kasr Alainy, Faculty of Medicine, Cairo University, and adhered to the Helsinki Declarations of biomedical ethics (Reference number MS-422-2020).

Results

A total of 29 patients seen at cystinosis clinic were screened for inclusion criteria which included children above 6 years old with confirmed nephropathic cystinosis and on cysteamine treatment for at least 1 year. Twenty of these patients were recruited in the study, while nine patients were excluded, 7/9 were excluded because they were below the age of 6 years, and 2/9 patients had started cysteamine treatment for less than 1-year duration. These patients were matched to 26 children with CKD.

Mean age of patients enrolled in cystinosis group was 10.97 ± 3.5 years, while the mean age of CKD group was 9.30 ± 2.6 years with no significant statistical difference between both groups. Consanguinity was significantly higher in the cystinosis group. There was no statistically significant difference between both groups regarding gender, body mass index (BMI), and CKD stage. The median age of onset of cystinosis was 6 months with interquartile range IQR (4 to 36 months), median age of diagnosis is 54.5 months with IQR (3 to 108 months), and percentage of affected siblings was 55%. All patients were on the maximum dose of cysteamine treatment (60 mg/kg/day), and most of them were compliant to the treatment (80%) (Table 1).

According to SB test, there was no significant difference in the intellectual functions between cystinosis and CKD groups (Table 2). In children with cystinosis, there was better IQ score in patients with CKD stage 1 compared with more advanced stages with no statistical significance (Table 3).

There was no significant difference between both groups regarding all categories of the CBCL questionnaire. Nevertheless, the control group showed a significant score for delinquent behaviour in comparison with cystinosis group.

In cystinosis group, 85% had internalization symptoms, 75% had somatic complaints in the form of abdominal pain or bony aches, 70% had withdrawn behaviour, and 50% was anxious or depressed (Table 4).

There was negative correlation between duration of cysteamine therapy and (short-term memory, sex

Table 1 Demographic and clinical characteristics of both groups

	Cystinosis group ($n = 20$)	CKD group ($n = 26$)	*T*-test/chi-square (t/χ^2) value	*p*-value
Age, years	3.5 ± 10.97	2.6 ± 9.30	$t = 1.819$	0.076
Gender				
Male	(40%)8	(50%) 13	$\chi^2 = 0.456$	0.561
Female	(60%) 12	(50%)13		
Consanguinity	(90%) 18	(34.6%) 9	$t = 14.303$	0.001 >
BMI, kg/m^2	4.1 ± 16.05	3.1 ± 15.86	$t = 1.041$	0.867
Serum creatinine (mg/dl)	0.6 ± 3.10	0.4 ± 2.54	$t = 1.146$	0.402
CKD stage				
I/II	(30%) 6	(30.8%) 8	$t = 0.684$	0.358
III/IV/V	(70%) 14	(69.2%)18		

Independent *t*-test was used to compare difference in mean between groups (t). Chi-square test was used to compare the difference in frequencies among groups (χ^2). *CKD*, chronic kidney disease; *BMI*, body mass index

Table 2 Comparison between cystinosis and CKD groups regarding Stanford-Binet test (SB)

	Cystinosis group ($n = 20$)	CKD group ($n = 26$)	*T*-test/chi-square (t/χ^2) value	*p*-value
IQ	81.25 ± 15.9	83.77 ± 15.5	$t = 0.283$	0.592
Average	7 (35%)	11 (42.3%)	$\chi^2 = 1.242$	0.209
Below average	3 (15%)	6 (23.1%)		
Mild MR	5 (25%)	5 (19.2%)		
Slow learning	5 (25%)	4 (15.4%)		
Verbal reasoning	82.85 ± 13.7	83.84 ± 10.2	$t = 0.189$	0.787
Visual reasoning	88.45 ± 11.6	92.04 ± 12.3	$t = 1.057$	0.319
Short-term memory	82.30 ± 14.8	82.58 ± 14.9	$t = 0.067$	0.950

Independent *t*-test was used to compare difference in mean between groups (*t*). Chi-square test was used to compare the difference in frequencies among groups (χ^2)
CKD chronic kidney disease, *IQ* intelligence quotient

Table 3 Comparison between IQ and different stages of kidney disease in cystinosis group

Chronic kidney disease stage (CKD stage)	IQ (median range)	Kruskal-Wallis test value (*f*)	*p*-value
Stage I ($n = 4$)	94.5 (75–95)	$f = 2.137$	0.680
Stage II ($n = 2$)	81.5 (78–85)		
Stage III ($n = 3$)	65 (59–105)		
Stage IV ($n = 4$)	78 (67–110)		
Stage V ($n = 7$)	78 (54–105)		

Kruskal-Wallis test was used for mean difference between groups *(f)*

IQ, intellectual quotient

Table 4 Comparison between cystinosis and CKD groups regarding Child Behaviour Checklist (CBC)

	Cystinosis group ($n = 20$)	CKD group ($n = 26$)	*T*-test/chi-square (t/χ^2) value	*p*-value
CBCL score	75.45 ± 7.8	76.77 ± 9.4	$t = 0.244$	0.608
• Nonsignificant	1 (5%)	2 (7.7%)	$\chi^2 = 0.359$	0.625
• Significant	19 (95%)	24 (92.3%)		
Withdrawn	66.80 ± 10.6	67.35± 11.2	$t = 0.108$	0.868
• Nonsignificant	6 (30%)	9 (34.6%)	$\chi^2 = 5.179$	0.073
• Significant	14 (70%)	17 (65.4%)		
Somatic complaints	73.20 ± 11.1	72.73 ± 13.8	$t = 0.124$	0.889
• Nonsignificant	5 (25%)	5 (19.2%)	$\chi^2 = 2.067$	0.365
• Significant	15 (75%)	21 (80.8%)		
Anxious/depressed	63.95 ± 5.6	64.04 ± 7.2	$t = 0.038$	0.986
• Nonsignificant	10 (50%)	14 (53.8%)	$\chi^2 = 1.849$	0.397
• Significant	10 (50%)	12 (46.2%)		
Social problems	60.95 ± 8.6	60.89 ± 7.8	$t = 0.027$	0.979
• Nonsignificant	14 (70%)	16 (61.5%)	$\chi^2 = 1.374$	0.503
• Significant	6 (30%)	10 (38.5%)		
Thought problems	58.85 ± 7.1	56.39 ± 8.6	$t = 1.036$	0.293
• Nonsignificant	12 (60%)	18 (62.2%)	$\chi^2 = 0.842$	0.675
• Significant	8 (40%)	8 (30.8%)		
Attention problems	60.65 ± 9.2	64.96 ± 11.1	$t = 1.411$	0.156
• Nonsignificant	13 (65%)	12 (46.2%)	$\chi^2 = 2.999$	0.202
• Significant	7 (35%)	14 (53.8%)		
Delinquent behaviour	55.90 ± 6.2	61.77 ± 8.5	$t = 2.586$	0.014
• Nonsignificant	17 (85%)	14 (53.8%)	$\chi^2 = 7.129$	0.028
• Significant	3 (15%)	12 (46.2%)		
Aggressive behaviour	62.25 ± 10.5	64.73 ± 11.6	$t = 0.748$	0.495
• Nonsignificant	12 (60%)	13 (50%)	$\chi^2 = 0.533$	0.766
• Significant	8 (40%)	13 (50%)		
Sex problems	51.40 ± 4.3	50.77 ± 3.9	$t = 0.518$	0.607
• Nonsignificant	19 (95%)	25 (96.2%)	$\chi^2 = 2.071$	0.639
• Significant	1 (5%)	1 (3.8%)		
Internalization	70.45 ± 6.5	71.01 ± 9.1	$t = 0.227$	0.821
• Nonsignificant	3 (15%)	4 (26.9%)	$\chi^2 = 1.012$	0.603
• Significant	17 (85%)	22 (73.1%)		
Externalization	59.70 ± 9.7	62.69 ± 11.2	$t = 0.949$	0.339
• Nonsignificant	11 (55%)	13 (50%)	$\chi^2 = 1.778$	0.411
• Significant	9 (45%)	13 (50%)		

Independent *t*-test was used to compare difference in mean between groups (t). Chi-square test was used to compare the difference in frequencies among groups (χ^2)

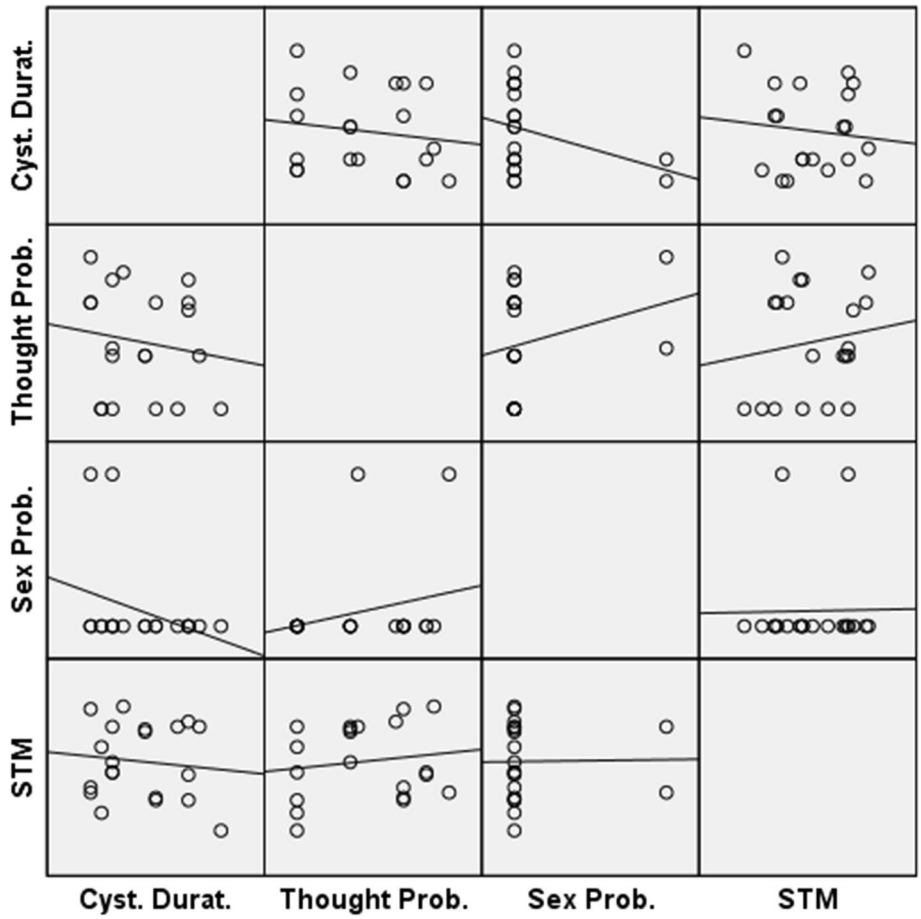

Fig. 1 Correlation between cysteamine therapy duration and short-term memory, sex problems, and thought problems. STM, short-term memory; cyst, cysteamine; sex prob, sex problems; thought prob, thought problems

problems, and thought problems) as tested by Pearson correlation test ($r = -0.376, -0.219, -0.408/p = 0.044, 0.041, 0.037$, respectively). One male child, 8 years old, had noted sexual problems (as preoccupation with sexual body parts and wishes to be of opposite sex, which were significant (score = 68). He was on cysteamine for 36 months at the time of assessment. Thought problems were found to be significant in 8 children, most of whom (5/8) were on cysteamine for duration of less than 12 months; twelve patients with NCTN had score on SB scale below 90 (below average) for short-term memory; they were on cysteamine treatment for duration ranging from 36 to 156 months (Fig. 1).

Discussion

In this study, we compared children with NCTN to age- and sex-matched children with CKD, to observe any significant differences in neurocognitive functions and behavioural profiles as most of previous studies compared them with healthy control to figure out if cystinosis apart from renal dysfunction can affect these functions.

In our study, there was no significant difference in the overall intelligence quotient between NCTN children and patients with CKD. Both groups had low total IQ score (below 90); however, higher percentage of children with NCTN (50%) compared to CKD group (33%) had mild mental retardation or slow learning, and this comes with conclusion made by Trauner and his colleagues who suggested that neurocognitive dysfunction cannot be attributed only to renal impairment [7].

In NCTN group, children with CKD stage 1 had median IQ score 94.5 tested by SB test that was higher than children with more advanced stages, but it was not statistically significant (p-value = 0.68). This may be due to the small number of patients with NCTN in each CKD stage, and this was consistent with the study that found IQ is positively correlated with eGFR [21] and another cohort study of 855 adults with CKD which concluded

that lower eGFR was associated with lower scores in most cognitive domains [22].

We found that there was no significant difference between both groups regarding emotional and behavioural problems tested by CBCL (total score 75.45 ± 7.8 and 76.77 ± 9.4, respectively with $p = 0.608$); this is contrary to an earlier study done in the same setting that reported a significant difference in emotional and behavioural problems in NCTN children compared to control (total score NCTN children 62.9 ± 7.9, control 48.1 ± 5.5 with $p = 0.004$) [21]. However, they compared NCTN children with healthy children not CKD children unlike our study. Additionally, all of our patients with NCTN were on cysteamine treatment for more than 1 year.

In our study, it was observed that the mean total score for behavioural and emotional problems was significantly high in NCTN children (75.45 ± 7.8). This supports a previous study reporting that children with cystinosis were at a higher risk for behavioural problems [23]. Delgado and colleagues compared NCTN children with healthy controls and cystic fibrosis children as they expected that chronic disease may have effects on behavioural and social functions; however, in our study, we demonstrated higher mean T score on CBCL (75.45 ± 7.8), especially regarding somatic complaints, withdrawn behaviour, and anxious/depressed behaviour [23]. This might be explained by low socioeconomic status, low schooling rate, and lack of psychosocial support observed in our cases.

In our study, we found a negative correlation between duration of cysteamine therapy and some items tested by SB test and CBCL (short-term memory, thought, and sexual problems). By increasing duration of cysteamine therapy, there was significant improvement in some behavioural functions (thought problems, sex problems). This is presumably due to the positive effect of treatment on thyroid and renal functions that can have an impact on behavioural functions [24]. Additionally, cysteamine prevents late complications of cystinosis, which includes neurological symptoms [25].

There was deterioration of some neurocognitive functions (short-term memory) by increasing the duration of cysteamine treatment, as observed in our study. This may be due to late initiation and lack of persistent treatment, as long-term studies have shown that when cysteamine was given early, it prevented neurocognitive dysfunctions [10–12].

Despite being on cysteamine treatment for 12 months or more, children with NCTN had poor performance on SB scale (score less than 90), so neurocognitive deficits cannot be explained by cysteine accumulation or even renal dysfunction (CKD group had better score for visual reasoning); this could raise the possibility of CTNS gene impact on brain function as evidenced by asymptomatic carriers of the gene, who have normal kidney functions and no cysteine accumulation, and demonstrated cognitive deficits similar to homozygous individuals with cystinosis [13].

Limitations

This was an analytical cohort study, we were unable to assess changes in neurocognitive function over time. Moreover, the small sample size in children with NCTN and CKD limited our ability to detect effects of variables such as eGFR, gender, and age on neurocognitive functions and behavioural profiles. Additionally, we did not take in consideration the social status and educational level of the parents that could have a large impact on their children's behavioural profiles. We did not employ a baseline psychometric assessment before the start of cysteamine therapy or objective monitoring of treatment compliance due to unavailability of WBC cysteine essay.

We suggest to perform this study on a large scale of children with NCTN with normal renal function, follow-up of these patients over a long duration of time, and to correlate this psychometric assessment to the onset of treatment, WBC cysteine assay, and type of genetic mutation.

Conclusions

Children with cystinosis have a wide range of neurocognitive deficits and behavioural problems. These deficits cannot be explained only by renal dysfunction and cysteine accumulation and could be a consequence of *CTNS* gene mutation and its effect on brain development. Longer duration of treatment could have beneficial effects on some of the behavioural problems.

All physicians dealing with this rare lysosomal disease should be aware of these neurocognitive and behavioural deficits and utilize suitable tools for baseline and scheduled assessments to provide multidisciplinary management.

Abbreviations

NCTN: Children with nephropathic cystinosis; CKD: Chronic kidney disease; CBCL: Child Behavioural Checklist; SB: Stanford-Binet test; CTNS: Cystinosin, lysosomal cystine transporter; CPNT: Center of Paediatric Nephrology and Transplantation; BMI: Body mass index; IQR: Interquartile range; IQ: Intelligence quotient; eGFR: Estimated glomerular filtration rate.

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Authors' contributions
FMA, methodology, patients' assessments, and sharing in writing the manuscript. *WRA*, methodology, patients' assessments, and sharing in writing the manuscript. *SHS*, methodology, patients' assessments, and sharing in writing the manuscript. *NAS*, research idea, methodology, and final revision of the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee, Kasr Alainy, Faculty of Medicine, Cairo University, and adhered to the Helsinki Declarations of biomedical ethics (Reference number MS-422-2020).

Consent for publication
Verbal and written informed consents were taken from the patients' guardians.

Competing interests
The authors declare that they have no competing interests.

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