Cognitive function assessment in adolescent patients on hemodiaylsis

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Background
Studying the impact of chronic kidney disease on neurocognitive functions is a critical element for providing optimal care to these children who might suffer from its detrimental consequence on their psychosocial life.
Aim
The aim of the study was to assess the cognitive functions in adolescents with end-stage renal disease (ESRD) under regular hemodialysis compared with healthy controls.
Patients and methods
We studied 40 adolescents – 20 patients with ESRD on regular dialysis and 20 controls closely matched with the patient in terms of their age, sex, and educational level. Patients were recruited from the pediatric dialysis unit, Menoufia University hospitals, with dialysis durations ranging from 0.5 to 8.5 years with mean 3.25 ± 2.28 years. They were assessed using Raven's Progressive Matrices tests (for fluid intelligence), and a computerized battery composed of Spatial Span (visual–spatial working memory task), Tower of London task (measuring planning and problem-solving ability), and the Go/No Go task (a task assessing response inhibition, set shifting, and attention). We, furthermore, assessed disease-related variables impacting the cognitive functions of the patients.
Results
The average age of the patients was 14.4 ± 3.315 years, and that of the controls was 13.7 ± 1.46 years. The fluid IQ for the patients was significantly lower than the controls ($P < 0.0001$): only nine patients were above average level of intelligence (≥75%). Patients tended to score lower on Spatial Span test compared with the controls (correct trials: 5.4 ± 1.81 vs. 7.55 ± 1.23; memory span: 3.6 ± 0.82 vs. 4.65 ± 0.81, respectively). In the Tower of London test, the patients' total number of correct trials was less than that of controls (5.78 ± 2.65 vs. 7.3 ± 1.75). Patients showed more Go errors than did controls ($P < 0.0001$) on the Go/No Go task. Patients' scores on Spatial Span test were influenced by lower hemoglobin concentration. In addition, hypertensive patients showed shorter start time in the Tower of London test and more P-No/Go error on the Go/No Go task. Neither duration of dialysis nor the urea reduction ratio significantly affected cognitive test.
Conclusion
Our findings provide evidence that the fluid intelligence and cognitive function of adolescents with ESRD on dialysis fall within the low average on most tasks. Furthermore, hypertension and anemia potentially place children with ESRD at an increased risk for neurocognitive deficits, which consequently places them at risk for poor long-term educational and occupational outcomes.

Keywords:
adolescents, assessment, cognitive, hemodialysis

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Introduction

Chronic kidney disease (CKD) is irreversible kidney damage that can further progress to end-stage renal disease (ESRD) in which the kidney function is severely compromised such that some type of renal replacement therapy is needed [1]. It is considered a major public health problem worldwide. ESRD is a devastating condition associated with excessive mortality and cardiovascular morbidity with specific problems occurring in children, such as impaired growth and psychosocial adjustment, which severely has impact upon their quality of life [2]. Most children with ESRD start on dialysis and then receive a transplant [3].

The incidence and burden of CKD in children and adolescents in Egypt is not known due to the absence of a national registry collecting data on ESRD. However , Safouh *et al.* [4] reviewed the records of 1018 Egyptian children

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patients (male patients 56.7%, age ranging from 1 to 19 years) suffering from CKD following-up at the pediatric nephrology units of 11 universities providing tertiary medical care to children from all Egyptian governorates over a period of 2 years. They reported that the most common cause of CKD was obstructive uropathy (21.7%), followed by primary glomerulonephritis (15.3%), reflux/urinary tract infection (14.6%), aplasia/hypoplasia (9.8%), and familial/metabolic diseases (6.8%); unknown causes accounted for 20.6% of the cases. Of the 587 patients who had reached ESRD, 93.5% were treated with hemodialysis (HD) and only 6.5% were treated with peritoneal dialysis.

Chronic HD is technically feasible in children of all ages. There are technical aspects of the procedure, and complications, that are unique to the pediatric population. And it is crucial that these differences should be recognized and addressed to effectively and safely perform pediatric HD, thereby reducing complications in children who are facing a lifetime of renal replacement therapy [5].

The relationship between CKD and neurodevelopmental dysfunction in children is well recognized [6,7]. Complications of CKD such as anemia, hypertension, and malnutrition are likely the key factors contributing to the cognitive deficits of children with CKD [8]. Cognitive functions have been shown to decline in patients on long-term HD [9]. Numerous theories have been postulated to explain the mechanism of this decline in cognition, which could be related to the fact that HD patients have underlying macrovascular disease (such as hypertension), which often present leads to recurrent cerebral ischemia resulted from the instability in the blood pressure with fluid loss and hemoconcentration inducing cerebral hypoperfusion occurring during HD session. Similarly, the PET scans have shown reduced cerebral blood flow and oxygen metabolism in HD patients [10]. They are also at an increased risk for having white matter disease, which is associated with deficits in executive cognitive domains [11].

In addition, HD is related to the recurrent delirious episodes with cerebral edema secondary to 'dialysis disequilibrium' syndrome, with fluid and electrolyte changes escalating cognitive impairment risk [12].

Cognitive impairment among HD patients raises patient safety concerns. Unfortunately, the data available on assessment of cognition in HD pediatric patients remain extremely limited. A better understanding of the cognitive functions of HD children is essential to make a precise and early diagnosis, which in turn might prove to be helpful in identifying the preventable or reversible causes of progression, predicting prognosis, and aiding the counseling of the children and their families, as these neurocognitive deficits undoubtedly will have significant lifelong implications for these group of patients as they move into adulthood.

Aim

The aim of the study was to assess the cognitive functions in adolescents undergoing HD and exploring the associations between neurocognitive function and clinical characteristics of HD patients.

Hypothesis

We hypothesized that children with ESRD receiving HD would perform less effectively than their healthy counterparts on cognitive functions tests.

Patients and methods

In this cross-sectional case–control study, patients were recruitment from Menoufia University hospitals, Egypt. All procedures were reviewed and approved by the Ethical Committee of the Faculty of Medicine, Menoufia University. Informed written consent was obtained from each participant before enrollment in the study.

Participants

Twenty patients were recruited from the pediatric dialysis center Menoufia University hospitals, Egypt, who had ESRD on regular dialysis, and 20 healthy controls who closely matched the patients in terms of their age, sex, and educational level, recruited from children of the employee working at Menoufia medical school and its hospitals. Inclusion criteria was age 11–18 years.

We targeted the adolescent group as they show better understanding and cooperation while doing cognitive tests; moreover, this age remains usually under-focused in research.

Patients were excluded if there was evidence of neurological disease that would impair cognitive functioning, those previously known to have learning disability, having any psychiatric disorders diagnosis, their renal impairment was a part of syndrome, and those refusing to give consent.

Following parental consent and patient assent, children meeting these criteria underwent neurocognitive testing just before starting their HD session. Laboratory sample collection were performed within a week of cognitive testing.

Characters of dialysis session and machine

The dialysis prescription was as follows three times per week, 4 h/session. Blood flow was 100–200 ml/min, with target urea reduction ratio greater than 65%, calculated as follows: Urea reduction ratio (predialysis urea – postdialysis urea)/predialysis urea.

Dialysis was performed with Fresenius 4008 S and B machines and hollow fiber polysulfone dialysis filters (Fresenius), using standard citrate dialysis solution.

Clinical measures of the studied group

Duration of dialysis, coded as time in years, Ca, PO_4, parathyroid hormone as well as the presence of anemia or hypertension were explored. Clinical data were obtained by physical examination, laboratory testing, and medical chart review.

Neurocognitive instruments

All participants completed a battery of intellectual, attention, and memory tasks as part of a neuropsychological evaluation, including the following:

(1) Raven metrics test: The Raven's Progressive Matrices tests are a collection of standardized intelligence tests that consist of geometric analogy problems in which a matrix of geometric figures is presented with one entry missing, and the correct missing entry must be selected from a set of answer choices. The entire Standard Progressive Matrices consists of 60 problems divided into five sets of 12 problems each (sets A, B, C, D, and E), roughly increasing in difficulty both within and across sets.
The Raven's Progressive Matrices assesses the ability to infer rules, to manage a hierarchy of goals, and to form high-level abstractions. As a paramount metric of reasoning and problem solving, the Raven's Progressive Matrices is believed to be a 'paradigmatic' measure of fluid intelligence that requires coordinated executive function, attentional control, and working memory [13].
(2) Spatial Span: a visual–spatial working memory task was obtained from the Psychology Experiment Building Language (PEBL) website. In this test, nine squares are depicted on the computer monitor and they light up one square at a time. Participants were asked to watch and recall how the squares light up in a forward order (increasing in span with successive trials) [14].
(3) The Tower of London task: it is classically used to measure planning and problem-solving ability by requiring participants to match a pattern by moving a series of colored discs with the goal of completing the problem in as few moves as possible [15].
A computerized version of the Tower of London task from the PEBL software package [16] was used. The Tower of London task requires the participant to match a pattern of three colored discs within a required number of moves. The display was divided into two halves. A target arrangement was presented in the upper half of the screen. A starting arrangement was presented in the lower half of the screen. Children were instructed to move the colored discs in the lower half of the display to match the pattern in the upper half of the display. There were 12 trials with a starting pattern requiring two, three, four, or five moves to achieve the target arrangement. The patterns increased in degree of difficulty, beginning with two-move problems and ending with five-move problems. The number of problems correctly solved were those solved in the minimum number of moves.
(4) The Go/No Go task: it is a response inhibition task where a motor response must either be executed or inhibited. During this task, participants were required to watch a sequential presentation of letters and respond to a target letter by pressing the right shift button. The presentation began with a 2×2 array with four stars (one in each square of the array).

A single letter (P or R) was then presented in one of the squares. In the first condition (P-Go), participants were asked to press the button in response to the target letter P and withhold their response to the nontarget letter R. A second, reversal condition (R-Go) was then administered, and participants were now asked to make a response to the target letter R and withhold their response to the nontarget letter P (the letter that they were initially conditioned to make a motor response to in the first, P-Go condition).

Prior to the task, the participants were administered a brief practice session to ensure the task was fully comprehended. Behavioral performance of the task was assessed by calculating four values in each condition: (a) correct responses to the target (Go) letter (hits); (b) errors of omission (misses) to the Go letter; (c) errors of commission (false alarms) (i.e. responding incorrectly to the No Go letter); and (d) correct rejections to the No Go letter.

In addition, response time (RT) to the Go letter was assessed for each participant. Go errors are typically considered as an indicator of in attention to the task, while No Go errors and RT to Go responses are considered as indicators of impulsivity [17]. A computerized version was obtained from the PEBL website [16]. In this version, only the means of correct responses were calculated for each parameter. Thus, instead of using P-Go errors or P-No/Go errors, correct P-Go and P-No/Go will be used and so on.

Statistical analyses

All analyses were done using the software SPSS 20. As variables were not normally distributed, the Mann–Whitney test was used to compare the results of patients and controls. Statistically significant findings were determined by a two-tailed P value less than 0.05. The χ^2-test was used to compare the percentages of male participants and female participants in both groups. Spearman's correlation test was used to assess the relation between Raven matrices scores and other variables.

Results

Demographic data

The study comprised 40 participants, including 20 patients on dialysis (eight male patients and 12 female patients), and 20 controls (10 male participants and 10 female participants). The mean age of the patients was 14.4 ± 3.315 years; the mean age of controls was 13.7 ± 1.46 years. There was no difference in the ages of the patients and the controls even when gender was taken into account, as shown in Table 1.

Patient clinical characteristics

Table 2 summarizes patient characteristics. Duration of dialysis was in the range 0.5–8.5 years, with mean 3.25 ± 2.28. Fourteen patients were hypertensive, receiving two to three drugs to control hypertension, whereas 6 patients were normotensive.

Comparison of patient' with controls' cognitive functions

Results of the Raven metrics showed that fluid intelligence ranks of controls were significantly higher than that of patients ($P < 0.0001$). All controls scored above average

Table 1 Comparison of patients and controls regarding age and sex

	Patient	Controls	Test	*P*
Age	14.5 ± 3.009	13.74 ± 1.466	Mann–Whitney $Z = -0.015$	0.988
Sex				
Male	8	10	$\chi^2 = 0.404$	0.525
Female	12	10		

Table 2 Patient clinical characteristics

Variables	Minimum	Maximum	Mean ± SD
Urea reduction ratio (%)	46	75	65 ± 0.07
Hemoglobin concentration	6.9	13.5	10 ± 1.8
Ca	6.89	10.5	8.69
PO_4	2.2	6.6	4.5 ± 1.1
Parathyroid hormone			
High	13	–	–
Normal	4	–	–
Low	3	–	–
Bone deformity			
Positive	13	–	–
Negative	7	–	–
Hypertension			
Positive	14	–	–
Negative	6	–	–

(i.e. ≥75%); similarly, only nine patients scored the same, while six patients' scores were at average level (25–50%); and the other five patients scored below average (≤25%), as shown in Table 2.

Moreover, the scores of controls were higher than that of patients in the Spatial Span test regarding both number of correct trials and memory span (Table 2).

Analysis of Tower of London testing results indicated that the total number of correct trials by patients were significantly lower than that of controls ($P = 0.041$). While the start time and total time of controls were longer than that of patients, there was no statistically significant difference between the two groups regarding practice time, as shown in Table 2.

Regarding the Go/No Go task, there were no statistically significant differences between the two groups in both No Go errors and RT to Go, and yet the patients recorded more Go errors in both test parts (R–P), with finally more number of errors and less correct responses than controls, as shown in Table 3.

Variables affecting cognitive functions

When we tried to explore how patients' clinical characteristics might pose potential risk on cognitive functions, analysis only showed association between hypertension, anemia, and cognitive functions.

A positive correlation was found between hemoglobin concentration and memory span in all patients. When we compared the scores of patients whose hemoglobin concentration was less than 9 with those with higher hemoglobin concentration, no differences were found between the two groups except for longer memory span in the second group. Moreover, hypertensive patients showed shorter start time and more P-No/Go error.

No correlations were found between urea reduction ratio, Ca, PO_4, parathyroid hormone, and duration of dialysis in cognitive tests, even when we compared the scores of patients with duration of dialysis less than 2 years with those with longer durations.

Discussion

Over the last two decades, the association between HD and CI has increasingly been of an interest in research [10]. As the prevalence of cognitive impairment is higher in individuals with renal failure when compared to the general population and even more significant in patients on dialysis [18]. Consequently, it interferes with the baseline functions possibly at a level enough to impair the performance of daily living activities [19], including school performance and interpersonal relationships.

We compared 20 adolescents on dialysis with matching healthy group to discern whether children with ESRD would perform less effectively than their controls on fluid intelligence, visual working memory, attention, planning and problem solving, response inhibition, and set shifting tests, and to determine whether different disease variables would influence such results.

Sarnak *et al.* [20] found that patients on dialysis performed more poorly than the general population on tasks assessing executive function; attention problems were especially particularly noteworthy as they can interfere with both the acquisition of new skills and the demonstration of their previously acquired skills [20], a finding which correlated with the present study, where the patients showed lower scores in the Spatial Span test, indicating problems in their visual working memory and attention, compared with the controls. Similarly, both Fennell *et al.* [21] and Gipson *et al.* [22] reported lower memory scores for children and adolescents (7.5–19 years) with CKD compared with controls. At the same time, they performed more errors in Go/No Go task due to their attention problem and showed inability to shift from P to R task; however, they were able to suppress response to an incorrect stimulus (intact inhibitory control), which was consistent with previous study conducted by Gipson *et al.* [22], showing that the CKD children group did not differ on response inhibition compared with the controls. In contrast, Gipson *et al.* [22] reported no differences in measures of sustained attention between children with HD and matched controls.

Regarding other executive functions, adolescents on HD showed a decrease in their planning and problem-solving abilities as determined by the Tower of London test compared with the controls, with less correct trails and less starting time as they not taking enough time to plan ahead before starting the task, a finding which was in line with Rasbury *et al.* [23], who noted in 14 children with ESRD difficulty in their problem-solving abilities.

Assessment of general cognitive function measured by the IQ was consistent with previous researches conducted on children with CKD, reporting that the

Table 3 Comparison of patients and controls scores on cognitive tests

Test	Patient	Control	Mann–Whitney	*P*
Raven matrices test	27.7 ± 10.63	49.6 ± 4.03	−4.816	0.0001
Spatial Span test				
Block span	4.2 ± 1.15	5.4 ± 1.05	−3.228	0.001
Total score	24.45 ± 10.45	41.85 ± 15.45	−3.954	0.0001
Correct trials	5.4 ± 1.81	7.55 ± 1.23	−4.093	0.0001
Memory span	3.6 ± 0.82	4.65 ± 0.81	−3.739	0.001
Go/No Go				
Total correct	269.05 ± 29.15	304.05 ± 8.66	−4.847	0.0001
Total error	50.95 ± 29.15	15.95 ± 8.66	−4.807	0.0001
Correct P-Go	0.852 ± 0.134	0.985 ± 0.018	−4.701	0.0001
Correct P-No/Go	0.92 ± 0.171	0.925 ± 0.136	−0.437	0.463
Correct R-Go	0.74 ± 0.252	0.982 ± 0.03	−5.045	0.0001
Correct R-No/Go	0.595 ± 0.252	0.7 ± 0.165	−1.289	0.197
Response time P-Go	569.66 ± 65.57	554.8 ± 79.13	−1.028	0.304
Response time R-Go	559.71 ± 168.28	603.19 ± 67.65	−0.649	0.516
Tower of London				
Total correct	5.78 ± 2.65	7.3 ± 1.75	−2.041	0.041
Total time	333.8 ± 185.17	507.25 ± 182.67	−3.14	0.002
Start time	161.15 ± 110.94	337.5 ± 117.34	−4.25	0.001
Practice time	172.6 ± 110.98	169.6 ± 105.8	−1.245	0.213

distribution of IQ scores is shifted downward compared with the normal population, with low-average (IQ 80–89) and average (IQ 90–109) range scores predominating [24–26]. We found that HD patients had lower fluid intelligence (showing their the capacity to reason and solve novel problems, independent of any knowledge from the past) compared with controls, with only nine patients showing above-average intelligence, whereas all controls depicted above-average scores. Similarly, Brouhard *et al.* [27] described a significantly lower nonverbal intelligence in children (13.7 ± 0.44 years) with kidney disease compared with their sibling controls, and also the study by Amr *et al.* [28], done on 12 children (13.5 ± 2.9 years) with CKD stage 5 on regular HD and 12 as controls who were assessed using the Wechsler Intelligence Scale for Children, who reported that the mean scores on the verbal, performance, and full-scale IQ were significantly lower in the children on dialysis than in healthy children.

The Fluid intelligence is affected because it requires coordinated executive function, attentional control, and working memory, which are all impaired in our patients.

On the other hand, Warady *et al.* [29] reported a relatively intact IQ in 19 children, with a mean age of 6.6 ± 1.3 years, who had ESRD from infancy, with 15 (79%) of 19 in the average range. Yet in his studied group, 13 (72%) of 18 achieved average verbal IQ scores, whereas only 10 (56%) scored in the average range in the nonverbal subtest, which is similar to the decline in the fluid intelligence in the current study, which was tested by using the nonverbal tests. The discrepancy may be due to methodological differences as patients were of different age groups and received peritoneal dialysis. Moreover, patients were not followed up later to assess for further deteriorations. The downward trend observed across all cognitive domains is explained by the findings documented by Qiu *et al.* [30], that patients with ESRD undergoing routine HD display clear-cut structural alterations with significant decrease in gray matter volume observed in the bilateral medial orbitoprefrontal cortices, bilateral dorsal lateral prefrontal cortices, and the left middle temporal cortex [30] – these regions can result in the dysexecutive syndrome [31]. Moreover, regions with gray matter volume reduction have significantly altered resting state functional connectivity with other brain regions [30].

Although we did not demonstrate a correlation of executive functions abilities with different disease-related variables, we still found association with hypertension and anemia, an observation consistent with the findings of some well-controlled studies [32–34].

Having hypertension contributed to more impairment on the Go/No Go task with more P-No/Go errors, which rates the response inhibition ability and attention. Similar findings were noted by Hooper *et al.* [35] where the Continuous Performance Test-II showed errors of commission indicating problem in inhibitory control seen in the hypertensive group of CKD patients. Furthermore, Lande *et al.* [36] showed that hypertension was significantly associated with lower neurocognitive scores representative of short-term memory, and attention and concentration problems. In contrast, Slickers *et al.* [37] did not demonstrate a significant deficit in attention and attributed this finding to their sample as the majority of children with CKD were on antihypertensive therapy, and thus any existing hypertension in their study sample was at least partially treated, thus significantly restricting the range of variance available for doing correlation analysis [37].

Anemia has been shown to slow the cognitive event-related potential in adults with CKD (mean hematocrit = 23.7%) and impair cognitive function among otherwise healthy children aged 6–11 years with hemoglobin levels less than 11.8 g/dl [38,39]. In the current study, lower hemoglobin concentration was associated with decline in Spatial Span test, affecting memory span. This was in agreement with Slickers *et al.* [37] who showed that time-averaged hemoglobin concentrations less than 10.5 mg/dl were associated with lower memory performance.

Although increasing length of HD treatment has been shown to be associated with cognitive impairment [40], we did not find correlation between duration of analysis and cognitive tests.

The relative lack of association between the CKD-related variables and neurocognitive functions in our study could be explained by the small size of our studied sample.

Conclusion and recommendations

In summary, we found that patients with ESRD have lower neurocognitive functions than do similarly aged controls. Anemia and hypertension were associated with the decline.

Hence, these data suggest that children with ESRD will have neurocognitive deficits that can be manifest in the school setting with decreased achievement. Therefore, the identification of patients with cognitive impairment is an important step in the process to improve their quality of life and mitigate the morbidities associated with this condition.

We recommend the need of more studies to highlight the possible strategies that may be used to delay or prevent the onset of cognitive impairment in patients with CKD.

Limitations

We acknowledge that our study is limited by its small sample size. Furthermore, we did not consider other factors that may have impact on cognition like the age of onset of the disease, etiology of ESRD, or the duration of illness, and also, we did not tackle the impact of cognitive functions on their academic achievement.

Conflicts of interest

There are no conflicts of interest.

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