Original Article

Neurocognitive Functions and Educational Outcomes in Children with Chronic Renal Disease.

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Abstract

Introduction: Chronic kidney disease (CKD) in children is a major global health problem. They are at risk for developing cognitive functions impairment more than adults due to the development of CKD during crucial stages of brain development.

Aim of the study: To assess the neurocognitive status and educational outcomes in children with CKD stages 2-5.

Methods: A cross sectional study was conducted on 75 patients with CKD, & 25 controls. Neurocognitive status was assessed using WIQ (Wechsler Intelligent Quotient), Benton Visual Retention Test (BVRT), computerized Wisconsin Card Sorting Test (WCST) and structural MRI Brain.

Results: Children with CKD had significantly lower total, verbal, performance IQ and a disability at visual memory and attention denoted by worse performance at BVRT compared to the healthy controls. Scores of CKD patients at WCST were worse than the control, thus denoting a disability at brain executive functions. For MRI, white matter lesions were reported in 2 patients on regular hemodialysis.

Conclusions: Children with CKD may have average to low-average cognition compared with the general population, with significant deficits at educational outcomes, visual memory, attention, & executive function.

Limitations: We could not assess the longitudinal change in cognitive functions with advancing CKD, as the study was a cross sectional one with relatively small sample size.

Implication of Practice: This study highlighted the importance of implementing changes in the routine care of children with CKD encouraging better nutrition and educational programs.

Keywords: Chronic renal failure, Intelligence Quotient, MRI Brain.

Running title: Neurocognitive functions and educational outcomes in children with chronic renal disease**.**

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Introduction

Patients with CKD are at risk for developing cognitive functions impairment. This may be due to increased risk of cerebrovascular diseases in these patients, which can be attributed to uremic toxins and hyperparathyroidism that results in vascular calcification, endothelial dysfunction and chronic inflammation of the cerebral blood vessels. Other contributing clinical variables include the age of onset of CKD, duration of renal dysfunction, the stage of CKD and the clinical complications of chronic renal disease such as anemia or hypertension during crucial stages of brain development **[1,2].** Regarding cognitive development; a deficit in attention and memory has been reported in these patients**[3,4]**. However the number of patients on hemodialysis recruited in these trials were limited**.** Regarding structural brain abnormalities detected by brain imaging, most data depend on studies of adult patients with scarce data in children **[5]**.

Methods

A cross-sectional study comprised 100 subject (8 -18 years); 75 children with CKD stages (2-5) diagnosed according to KDIGO guidelines **[6]** and 25 healthy age and sex matched controls. All children were enrolled from the nephrology unit at our hospital from April 2018 to March 2020. Children were excluded if they had a history of perinatal injury, ischemic, traumatic brain injury, global developmental delay due syndromes with known primary neurological illness, systemic diseases that can affect the brain, and those who had renal transplantation. An informed written consent was obtained from the legal guardians of each child before enrollment. 100 subjects were divided according to the GFR into the following subgroups with 25 patients in each group: Group **(A)**: CKD stages 2 -3, Group **(B):** CKD stages 4 and 5 (just before starting dialysis), Group **(C)**: CKD Stage 5 on regular hemodialysis and Group **(D):** age and sex matched healthy controls recruited from the outpatient clinic as they were attending with their sick siblings.

All groups were subjected to the following measures

(1) Detailed medical history, including educational status: The Socioeconomic status (SES) was calculated using Fahmy et al. (2015) score **[7]**. Total score is 54 depending on six items; parents' education and occupation, family size, crowding index, family income, home sanitation and use of computer. The scores were stratified into high SES if > 40, middle if SES 27-40, and low SES if < 27.

(2) Thorough clinical examination, and laboratory investigations: Hemoglobin level, serum total calcium, phosphate, albumin, and parathyroid hormone (PTH) were measured. Glomerular Filtration Rate (GFR) was measured and calculated for CKD patients and the controls respectively.

(3) Study tools: Assessment for pediatric patients on Hemodialysis (HD) was done before their hemodialysis session. Cognitive assessment was done by a psychologist at the psychiatry institute of our hospital through:

a) IQ using Arabic validated version of Wechsler intelligence Scale revised for children & adults Wechsler Intelligence Scale for Children third edition WISC-III with age ranges from 6 to 16 years, and Wechsler Adult Intelligence Scale WAIS-

III for those who are 16 years old or more [8].

b) Benton Visual Retention Test (BVRT) form C [9]. It consisted of 10 designs and each one was exposed for ten seconds to the child. The card was removed, then the child was asked to draw what he had seen using his memory. The child's scores were compared with the expected scores found in the norm tables. The larger the difference, the more probable it is that the examinee has a neurological impairment of visual memory and attention.

c) Computerized Wisconsin Card Sorting Test (WCST) for recognizing executive functions of frontal cortex (planning – shifting – cognitive flexibility – sustained attention). A computer-based test was used, in which 4 stimulus cards appeared on the screen, with symbols differing in color, shape, and number. A fifth card was presented to the child, and the child was asked to match the card presented with one of the 4 stimulus cards and sort it under the most suitable stimulus card. The examiner declared if this match is right or wrong and accordingly the child kept or changed his chosen strategy for the following 128 cards. The indices chosen for assessment were (total trials administered, total correct trials, total errors, preservative response, non-preservative response, trials to complete first category, categories completed, failure to maintain set. The test is normal if the number of categories completed is 6 [10].

d) Awake non-contrast structural MRI Brain. MR data were obtained on a Philips Achieva 1.5 T MR scanner using a 16-channel Neuro-Vascular (NV) coil. Special comment on volume (cm3) of hippocampus, caudate, putamen, globus pallidus, amygdala, and nucleus accumbens (cm3) on both sides. Also, hippocampal blood flow was measured by Arterial Spin Label (ASL) (ml/ 100gm/ minute). The raw images were used to produce Cerebral Blood Flow (CBF) maps in units of mL/100 g/minute at hippocampus by taking three measurements for each side and the average reading was recorded.

Statistical Analysis

The collected data was revised, coded, tabulated and introduced to a personal computer using Statistical package for Social Science (SPSS 20).

Results

The mean age of CKD patients was (13 ± 2.68) years which was comparable to that of the controls (14.6 ± 2.79). (Table 1) shows the details of the socioeconomic status and school performance among the studied children. As regards the habitat, most of our patients (60%) were living in urban areas. Regarding the (SES), 56% of the patients were low SES, (32%) of the patients were middle SES. Regarding school performance, the number of children who repeated school grades, those with school absence, and those who dropped out school were significantly higher in group C in comparison to groups A, B, & D as shown in (table 1). Forty one percent of our CKD patients were hypertensive. The number of patients with systolic hypertension in groups A, B, & C was (7, 11, and 13) respectively. The number of patients with diastolic hypertension in groups A, B, & C was (8, 8, and 12) respectively. Both systolic & diastolic

blood pressure were significantly higher in group C in comparison to the other groups despite using a combination of antihypertensive drugs. Two patients in group D had blood pressure more than normal ranges. Fifty-four percent of our CKD patients were underweight, and 60% were stunted. Most of CKD patients in group C were underweight (23/25). However the number of underweight children in groups B and A was (14/25) and (4/25) respectively. Many of our patients had stunted growth, the number of patients who were below the third percentile was significantly the highest among group C (22/25). However, their numbers in groups B, & A were (14, 9) respectively. As regards laboratory investigations, there was a statistically significant difference among the CKD groups regarding haemoglobin level, serum calcium, phosphorus, and parathyroid hormone as shown in **(table 2)**.

Outcomes

The mean total IQ of our CKD patients was significantly lower compared to the control group, (88 ±11.05) & (108.6 ± 9.5) respectively. Forty-five percent of our CKD patients had low average total IQ, 38 % had average total IQ, while 14% had borderline or extremely low total IQ. **(Table 3)** demonstrated that Group C had the lowest mean total IQ. The total, verbal and performance IQ were lower in groups A, B, & C in comparison to group D. Analysis of the WIS, shows that the deterioration in performance IQ was more pronounced than that of verbal IQ . This was also found in groups B and C as well. In group (A) certain verbal and performance IQ subsets were more affected than others as shown in **(table 4).** VIQ scores were significantly higher in children with higher SES (P= 0.006) noting that most of the studied patients following in our governmental hospital were of low or middle SES. IQ was also significantly higher in children who did not drop out of school (P < 0.0001) and in those who did not repeat grades (P=0.018). IQ was negatively correlated with school absence (r = - 0.377, P = 0.001), duration of CKD (r = 0.287, P = 0.013) and PTH level (r = - 0.374, P = 0.001). It was positively correlated with hemoglobin levels (r = 0.266, P = 0.021). Neither blood pressure nor GFR was significantly associated with intellectual dysfunction. Thirty-seven % (28/75) of our CKD patients had a disability at visual memory and attention denoted by worse performance at BVRT. Worse performance in BVRT "disability" is defined by an obtained "correct" score ≥3 points lower than the expected score or an obtained "error " score ≥4 points higher than the expected one. The number of children with a high difference between the obtained and expected "correct" (worse performance) and the number of children with disabled Benton "error" scores were the highest in group C in comparison to other groups as shown in **(table 5).** Scores of children with CKD at WCST were worse than the control, thus denoting a disability at executive functions and visual spatial working memory of the brain, represented by more trials administrated to complete the test, more errors, more failed trials to complete the six card classification categories, and more failure to maintain set. This function seemed to deteriorate with the progression of the CKD to become the worst in group (C) as shown in **(table 6)**.

Table 1 : Total sample distribution within the different groups according to their socioeconomic status, school performance and duration of CKD.

		Group A (25)	Group B (25)	Group C (25)	Group D (25)	Chi square	P value
Habitat	**Rural**	3	2	6	3	4.39	0.64
	Suburban	7	9	4	6		
	Urban	15	14	15	16		
Care Giver Education	**Illiterate**	13	10	15	12	14.1#	0.22
	Primary/ read and write	7	4	3	9		
	Preparatory	2	1	1	2		
	Secondary	0	1	0	0		
	College/institute	3	9	6	2		
Care giver occupation	**Unemployed/ House wife**	11	5	9	8	7.35	0.29
	Manual worker	11	12	9	14		
	Governmental	3	8	7	3		
Socio economic status (SES)	**Low**	13	14	16	13	6.9#	0.33
	Middle	8	10	4	10		
	High	4	1	5	2		
Child Education Grade	**Primary**	12	9	15	5	19.8#	0.002*
	Prep	11	14	7	8		
	Secondary	2	2	3	12		
Grade Repetition	**No**	22	21	17	25	10.27#	0.016*
	Once	3	4	8	0		
School Drop Out	**No**	22	16	10	25	26.9	<0.0001*
	Yes	3	9	15	0		
School absence > 1 month in last school year	**No**	11	3	0	21	43#	0.00001*
	Yes	14	22	25	4		
Duration of CKD (years)	**Mean SD**	3.32 ± 2.07	3.12 ± 3.51	5.68 ± 2.89		6.05 ##	0.004*

*Statistically significant # Fisher's Exact test ## F ANOVA test.

MRI Brain

There was no micro-bleeds or cerebral infarcts in any case of our study. Regarding white matter lesions, we reported only 2 cases (4%) in group C with no neurological symptoms or signs. There were no cases of generalized brain atrophy. However, there was one case in group (A) who had appreciated volume loss of left hippocampus and medial temporal lobe atrophic changes. During the statistical analysis of brain volumetry, group A was excluded from the analysis as the number of patients who underwent brain imaging was not sufficient to include in the analysis. There was no statistically significant difference between CKD groups B & C and the control group regarding the volumetry of different regions of interest except for the left caudate. Group C had the highest mean 3.68 ± 0.52 cm^3. There was no statistically significant difference between CKD groups B & C and the control group regarding hippocampal perfusion. The hippocampal volume, on the right and left sides, were negatively correlated with the duration of the CKD ($r = -0.325$, $P = 0.021$) & ($r = -0.401$, $P = 0.004$) respectively. Left hippocampal perfusion was negatively correlated with PTH level ($r = -0.278$, $P= 0.029$). Also right and left hippocampal perfusion were positively correlated with the GFR ($r = 0.282$, $P=0.026$) & ($r = 0.294$, $P = 0.020$) respectively.

Table 2 : Clinical and laboratory data of the studied group

	Group A (25)	Group B (25)	Group C (25)	Group D (25)	Test	P-value
Age (years)						
Mean	11.45	13.04	14.6	14.6	8.06#	<0.0001*
SD	± 1.93	± 2.31	± 2.75	± 2.79		
No of children with systolic hypertension	7	11	13	2	34.4**	<0.0001*
No of children with diastolic hypertension	8	8	12	1	25.4**	<0.0001*
No of children with weight percentile < 3rd	4	14	23	0	66.5**	<0.0001*
No of children with height percentile < 3rd	9	14	22	0	49.1**	<0.0001*
Hemoglobin (gm/dL)						
Mean	10.30	9.09	9.42	10.01	3.39#	0.021*
SD	±1.83	±1.77	±1.23	± 0.92		
Calcium						
Mean	8.32	7.85	8.50	9.23	6.56#	<0.0001*
SD	±1.061	±1.19	±1.24	± 0.79		
Albumin						
Mean	3.35	3.95	3.79	4.12	10.5#	<0.0001*
SD	±0.53	± 0.47	±0.45	±0.61		
Phosphorus						
Mean	5.83	6.16	6.57	4.87	5.38#	0.002*
SD	±1.31	±1.82	± 1.76	±1.24		
Alkaline phosphatase (90-310 U/L)						
Mean	276.48	351.80	298.16	217.32	3.47#	0.19*
SD	± 84.24	±191.4	±190.7	±92.00		
Parathyroid Hormone (15-65 pg/ml)						
Mean	153.56	670.62	654.21	43.08	22.66#	<0.0001*
SD	±112.38	±533.5	±423.9	±13.09		

*Significant ** Chi Square # F ANOVA Test

Table 3 : Total, Verbal, Performance IQ in the studied groups

Parameter	Group A (25)	Group B (25)	Group C (25)	Group D (25)	F #	P value
Verbal IQ						
Mean	95.6	93.08	89.4	107.04	18.36	0.0001*
SD	± 7.96	± 10.04	± 11.9	± 8.04		
Performance IQ						
Mean	91	89	82	108.2	21.61	0.0001*
SD	± 10.7	± 7.6	± 15.09	± 11.9		
Total IQ						
Mean	92.8	90.56	83.5	108.6	27	0.0001*
SD	± 7.9	± 8.1	±13.9	± 9.5		

*Significant

Table 4 : Comparison of IQ subsets between CKD groups &the controls, 95% confidence interval (Cl)

Parameter	Mean difference between groups (A) & (D)	Mean difference between groups (B) & (D)	Mean difference between groups (C) & (D)
Verbal IQ	-11.44	-13.96	-17.64
95 % CI	[-15.97, -6.90]	[-19.13, -8.78]	[-23.41, -11.86]
Comprehensive	-2.7	-4.1	-4.7
95 % CI	[- 3.95, - 1.44]	[-5.19, -3.00]	[-5.809, -3.591]
Arithmetic Ability	-2	-2.5	-4.2
95 % CI	[- 3.025, - 0.975]	[-3.753, -1.247].	[-5.492, -2.908]
Similarity	-0.9	-1.42	-2.2
95 % CI	[-1.88, -0.08].	[-2.49, -0.34].	[-3.417, -0.983]
Digit span	- 3.8	-3.8	-4.9
95 % CI	[-5.32, -2.27]	[-5.32, -2.27].	[-6.59, -3.20]
Performance IQ	- 17.2	-19.2	- 26.2
95 % CI	[-23.63,- 10.76]	[-24.87, -13.52].	[- 33.9, - 18.5]
Picture completion	- 3.1	- 2.7	-4
95 % CI	[-4.21, -1.98]	[- 3.77, - 1.62]	[-5.21, - 2.78]
Block design	-1.7	-1.7	-2.6
95 % CI	[- 2.43, - 0.961]	[-2.43, -0.96]	[- 3.36, -1.83]
Coding	- 4.1	-5.2	- 6.6
95 % CI	[-6.09, - 2.10].	[-7.12, - 3.27]	[- 8.76, - 4.43]
Total IQ	-15.8	-18.04	-25.1
95 % CI	[-20.76, - 10.83]	[- 23.06, -13.01]	[-31.87, -18.33]

Table 5 : Benton Visual Retention test scores in the studied groups.

		Group A (25)	Group B (25)	Group C (25)	Group D (25)	Chi square	P value
Difference between obtained correct and expected correct #	Normal	12	10	9	13	5.527	0.478
	Borderline	7	7	6	9		
	High	6	8	10	3		
Difference between obtained error and expected error ##	Normal	14	12	9	19	29.06**	<0.0001*
	Borderline	6	6	0	6		
	High	5	7	16	0		

* Significant **Fisher's exact test

#Difference between obtained correct and expected correct (expected norm for age and Total IQ score)

Borderline is defined by Obtained correct (OC) scores being 2 points below Expected correct (EC).

High "disabled" is defined by Obtained Correct scores being ≥ 3 points below EC.

Difference between obtained error and expected error (expected norm for age and Total IQ score)

Borderline is defined by Obtained Error (OE) scores being 3 points higher than Expected Error (EE).

High "disabled" is defined by Obtained Error (OE) being were ≥ 4 points higher than Expected Error (EE).

Table 6 : Wisconsin Card sorting test among the studied groups.

Wisconsin	Group A (25)	Group B (25)	Group C (25)	Group D (25)	F #	P-value
No of Trials administrated Mean SD	112.6 ± 19.58	113.8 ± 21.59	122.1 ± 13.42	82.2 ± 12.51	25.76	<0.0001*
Total Correct Mean SD	71.9 ± 14.39	73.3 ±11.90	68 ± 15.55	68.2 ±6.57	1.12	<0.342
Total Errors Mean SD	40.6 ± 24.08	40.56 ± 20.85	54 ± 22.35	14.08 ±6.87	17.92	0.0001*
Preservative Response Mean SD	21.92 ± 31.11	17.32 ± 23.34	19.12 ± 30.53	9.68 ± 4.45	1.11	0.347
Preservative Error Mean SD	17.24 ± 23.60	13.40 ± 18.05	14.68 ± 23.17	7.08 ± 3.45	1.30	0.278
Non- Preservative Error Mean SD	23.44 ± 18.75	26.84 ± 18.10	39.32 ± 25.06	7.00 ± 5.33	13.27	<0.0001*
Completed Categories Mean SD	4.68 ± 1.81	4.36 ± 1.65	3.60 ± 1.89	6.00 ± 0	10.41	<0.0001*
Trials to First Category Mean SD	18.16 ± 23.89	17.88 ± 18.07	24.56 ± 28.62	11.84 ± 1.62	1.57	0.20
Failure to maintain set Mean SD	0.80 ± 0.81	1.36 ± 1.28	1.16 ± 0.89	0.40 ± 0.64	5.03	0.003*

Standard deviation (SD), *statistically significant, #Test used ANOVA

Discussion

In children and adolescents with CKD, evidence regarding the effect of reduced kidney function on neurocognitive functions varies substantially across studies. Regarding the intelligence quotient (IQ) test, we found that the mean total IQ of our CKD patients was significantly lower in comparison to the control group. Forty-five % of all CKD patients had low average total IQ, 38 % had average total IQ, while 14% had borderline or extremely low total IQ. The results of the present study are matching with a systematic review conducted in 2018 including 34 observational studies of 3086 children with CKD aged 21 years old or younger. This review showed that children with CKD have average to low average full-scale IQ scores compared with the population norm **[11].** Regarding different stages of CKD, we found that 60% of children in group C had average or low average TIQ, while 40% had borderline or extremely low total IQ. In groups A and B, most of the children (24/25) had average to low average TIQ, while only (1) child in each group had extremely low total IQ. So it is worth noting to mention that TIQ scores decrease with the progression of the CKD. As regards other studies selectively recruiting children with CKD on regular

dialysis, their results were similar to ours and reported that their cohorts' mean total IQ was lower than their matched controls or population norms **[12–14].** However some studies reported that the mean TIQ scores of their cohorts were not statistically different that the norm population**.** Mendley & Zelko (1999) recruited only 9 patients of mean age 14.2 ± 3.5 years with CKD; 5 on peritoneal dialysis, 3 on hemodialysis, and one patient with preemptive kidney transplantation. The mean IQ was within average range (91.6 ± 16) which was not statistically different from their norm population of mean IQ =100 and SD =15. The mean TIQ of their cohort was higher than ours. This can be attributed to small sample size, also the authors excluded any patient with TIQ less than 70 **[15].**

As regards studies recruiting children with ESRD, their results were similar to ours and reported that their cohorts' mean total IQ was lower than their matched controls or population norms**.** Bawden et al. (2004) compared 21 patients with ESRD (GFR < 18 ml/min/1.74 m ^{2}) with their sibling controls. All patients were on a renal transplant waiting list and either pending dialysis or on dialysis therapy either hemodialysis or peritoneal dialysis. Full Scale IQs of patients with ESRD were in the low average range (87.9 ± 2.7), but were significantly lower than the IQs of the sibling controls which were in the average range (98.8 ±2.2) **[16]**. Evidence regarding the effect of reduced kidney function on neurocognitive functions in patients with CKD managed conservatively varies across different studies. Our results agree with Amr et al. (2013) who reported that children with predialysis stages of CKD had lower overall IQ test scores in comparison to their matched controls **[12]**. However, our results are different from others who reported that these patients' scores were within age-appropriate expectations for IQ or were at a nearly normal developmental level for their norm population **[2,13].**We observed that both VIQ and PIQ were lower in CKD patients than their matched controls. However the deterioration in PIQ was more pronounced than that of the VIQ in all CKD groups. Lower PIQ scores denote that these children had disabilities to think and reason abstractly and solve problems. The development of this ability is considered independent of learning, experience, school education, verbal and cultural content **[17].** Similarly, some studies demonstrated that VIQ & PIQ of CKD patients were lower than their matched controls **[12,16]**. We found that the VIQ was significantly higher in children with higher SES, as the VIQ reflects the language and general culture more than the PIQ **[17].** In the present study, children who did not drop out of school, did not repeat grades, and those with lesser duration of school absence had significantly higher scores of TIQ, VIQ, & PIQ. It is noteworthy to mention that VIQ is good predictor of school achievement **[17].**

Also ongoing dialysis sessions for children with ESRD may reduce the amount and regularity of time spent in the classroom, with chronic absenteeism potentially preceding loss of interest, withdrawal, and poor school progression **[18].** Prolonged duration of CKD was associated with worse TIQ & VIP scores in our CKD patients. This was consistent with Slickers et al. (2007) results that demonstrated that the greater the percent of life with CKD, the lower the IQ score

[19]. We found that the IQ scores of our CKD patients were positively correlated with hemoglobin levels. CKD related anemia may reduce the delivery of oxygen to the brain and alter brain metabolism **[20].** However Slickers et al. (2007) reported that the presence of anemia did not correlate with differences in IQ test result between study participants with or without anemia. This may be because only three patients had a hemoglobin level below 11 gm/dl. Consequently, they were unable to assess anemic patients across a wide range of hemoglobin values **[19].** Also the IQ scores of our CKD patients were negatively correlated with serum levels of parathyroid hormone. The link between PTH and neurocognitive functions can be explained by the vascular damage theory. Elevated serum phosphate, elevated calcium phosphate product and parathyroid hormone (PTH) lead to accelerated endothelial dysfunction, and thus vascular calcification especially those of the brain **[21]**. Also it is speculated that secondary hyperparathyroidism can potentially interfere with neurotransmission by increasing calcium levels in the brain **[22].** Unlike our study, Yokoyama et al. (2020) reported in an update of the Chronic Kidney Disease in Children (CKiD) study that PTH Z-scores did not associate with IQ test scores in a cohort of 891 children aged 1 to 16 years with an eGFR between 30 and 90 ml/min per 1.73 m^2 at 54 centers across North America **[23]**. However they did not include children on dialysis or those with severe CKD with GFR less than 30ml/min/1.73 m^2. Regarding other neurocognitive functions, we demonstrated that 37% of our CKD patients had a disability at visual memory and attention denoted by worse scores at BVRT. Group C performed significantly worse in comparison to the other CKD groups at BVRT. As for WCST, groups A, B, & C performed significantly worse in comparison to the control group. We also found that the executive brain function and visual spatial working memory deteriorated with the progression of the CKD to become the worst in the dialysis group. Similarly Hartung et al. (2016) reported deficits of verbal working memory, and attention in children and young adult patients with CKD aged 8-25 years (73 CKD patients & 57 controls) using computerized neurocognitive battery of 14 tests **[24].** A systematic review including 13 observational studies (n=1366) of children with CKD aged 21 years old or younger to asses attention. Children with CKD had attention deficits and reduced visual and verbal memory compared with children without CKD **[11].** Unlike the current study some studies have found no significant differences in memory (verbal and nonverbal) between children with and without CKD. Bawden et al. (2004) found that the memory of patients with ESRD and the sibling controls was comparable **[16]**. For executive function, eleven studies with 1390 patients were included in Chen et al. (2018) which concluded that children with CKD had reduced planning skills **[11].**

Regarding MRI brain, we reported white matter lesions in two patients with CKD on regular dialysis, which was less than that reported by Matsuda-Abedini et al. (2018) **[25].** They reported focal and multifocal white matter injuries in children with early stages of CKD rather than children on dialysis, in 21 % compared to 4% in our study. Unlike our study, they included post renal transplant

patients. We did not observe silent infarcts nor microbleeds in any case of our study. Unlike Albaramki, Al-Ammouri & Akl (2016) who reported abnormal brain imaging in 27%, brain hemorrhage in 13%, and brain infarcts in 10 % of 68 children with end stage renal disease. This study recruited patients with vasculitis and this may explain the high incidence of abnormal brain imaging **[26].** There was no cases of global cerebral atrophy among our studied patients. However, one case with CKD stage 3 was reported to have temporal lobe atrophy. Hartung et al. (2018) reported that the whole-brain, cortical, and left parietal grey matter volumes were smaller in children and young adolescents with CKD than their matched than controls **[27].** Regarding specific areas of interest related to memory and attention, our study showed that there was no statistically significant difference between CKD patients and the control group apart from the left caudate which was surprisingly larger in size in the dialysis group than in the control group. It is worth noting to report that in our study, the hippocampal volume was negatively correlated with the duration of the CKD. Regarding blood flow to hippocampus there was no statistical significant difference between CKD patients and the control group. We found that hippocampal perfusion on both sides was negatively correlated with the GFR, and left hippocampal perfusion was negatively correlated with the PTH.

To date, no studies have investigated blood flow velocities in children with CKD. Hartung et al. (2018) reported that patients with CKD including both children and young adults aged 8-25 years (73 CKD patients & 57 controls) showed higher global CBF compared with control subjects that was attributable to reduced hematocrit level **[27].**

Conclusion

Children with CKD may have poor neurocognitive functions and reduced educational achievements compared with healthy children and this was more evident with the progression of the kidney disease especially among those on hemodialysis.

Abbreviations

CKD	Chronic Kidney Disease
WIQ	Wechsler Intelligence Quotient
BVRT	Benton Visual Retention Test
WCST	Wisconsin Card Sorting Test
MRI	Magnetic resonance Imaging
KDIGO	Kidney Disease Improving Global outcomes
SES	Socioeconomic Status
GFR	Glomerular Filtration Rate
PTH	Parathyroid hormone
HD	Hemodialysis
WISC	WISC-III
WAIS	Wechsler Adult Intelligence Scale
TIQ	Total Intelligence Quotient
VIQ	Verbal Intelligence Quotient
PIQ	Performance Intelligence Quotient

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Statements

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This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of our pediatric department of Ain Shams University. An informed written consent was obtained in every case from their legal guardians.

Consents for publication
The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material
The data and the material are genuine.

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