Duration of chronic kidney disease reduces attention and executive function in pediatric patients

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Chronic kidney disease (CKD) in childhood is associated with neurocognitive deficits. Affected children show worse performance on tests of intelligence than their unaffected siblings and skew toward the lower end of the normal range. Here we further assessed this association in 340 pediatric patients (ages 6–21) with mild–moderate CKD in the Chronic Kidney Disease in Childhood cohort from 48 pediatric centers in North America. Participants underwent a battery of age-appropriate tests including Conners' Continuous Performance Test-II (CPT-II), Delis–Kaplan Executive Function System Tower task, and the Digit Span Backward task from the age-appropriate Wechsler Intelligence Scale. Test performance was compared across the range of estimated glomerular filtration rate and duration of CKD with relevant covariates including maternal education, household income, IQ, blood pressure, and preterm birth. Among the 340 patients, 35% had poor performance (below the mean by 1.5 or more standard deviations) on at least one test of executive function. By univariate nonparametric comparison and multiple logistic regression, longer duration of CKD was associated with increased odds ratio for poor performance on the CPT-II Errors of Commission, a test of attention regulation and inhibitory control. Thus, in a population with mild-to-moderate CKD, the duration of disease rather than estimated glomerular filtration rate was associated with impaired attention regulation and inhibitory control.

Kidney International advance online publication, 24 September 2014; doi:10.1038/ki.2014.323

KEYWORDS: CKD; Conners' Continuous Performance Test; neurocognitive function; renal disease

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Received 7 October 2013; revised 28 July 2014; accepted 31 July 2014

Chronic kidney disease (CKD) in adults is associated with cognitive impairment, which may be related to kidney function, as measured by glomerular filtration rate (GFR) and the presence of albuminuria.[1–5] Possible mechanisms for cognitive impairment include accelerated cerebrovascular disease with ischemia, subclinical stroke, and subcortical atrophy[6–8] mimicking the pattern of age-related cognitive decline. However, the effects of CKD on cognitive function in childhood are clearly different. Childhood and adolescence are periods of brain growth and the development of neural pathways responsible for comprehension, memory, planning, problem-solving, abstract reasoning, and attentional control; decreased GFR or other effects of chronic illness may adversely affect these normal developmental processes.[9,10] Measuring these effects in children needs to be approached differently than is done in adults.

The early literature on childhood CKD shows its association with encephalopathy and developmental delay, especially of gross motor skills and language acquisition.[11–14] Case series show that when the uremic milieu coincides with critical periods of brain development it can cause nonspecific electroencephalogram abnormalities,[15,16] as well as structural changes including atrophy and infarcts.[17–19] Such severe deficits have become less common with the elimination of oral and dialytic aluminum intake and the avoidance of uncontrolled uremia.[20,21] Nonetheless, there remains evidence for subtle neurocognitive deficits in children with advanced CKD. Children with CKD perform less well on standardized tests of intelligence and academic achievement than their unaffected siblings.[22] Prospective studies have demonstrated that cognitive deficits can improve after kidney transplantation.[23,24] Lawry *et al.*[25] showed better neurocognitive function and school performance among transplant patients when compared with chronic dialysis patients.

Neurocognitive impairment has been described in other chronic diseases of childhood, including systemic lupus erythematosus, juvenile rheumatoid arthritis, inflammatory bowel disease, and cancer chemotherapy. Estimates of neurocognitive impairment in childhood systemic lupus

erythematosus vary depending upon the test battery used, the cohort and controls studied, and the categorization of cognitive impairment. Two studies demonstrated incidences of impairment ranging from 59 to 71% of small study groups.[26,27] In a prospective study with age- and ethnicity-matched controls in addition to standardized norms, systemic lupus erythematosus subjects and controls performed similarly.[28] Subjects with renal disease were overrepresented in the group with neurocognitive impairment, but this did not reach statistical significance. A study of 31 subjects with systemic juvenile rheumatoid arthritis showed no difference in Wechsler Intelligence Scale for Children Fourth Edition Revised (WISC-R) and Wechsler Adult Intelligence Scale Fourth Edition Revised (WAIS-R), information processing speed, memory, and verbal learning when compared with an age-matched and socioeconomically matched control group.[29] Adolescents with inflammatory bowel disease made more errors in tests of verbal learning than a comparable group with juvenile rheumatoid arthritis, yet performed similarly on other tests of memory, intelligence, and executive function (EF).[30]

The neurotoxic effects of chemotherapy for childhood cancer have been extensively studied. Risk factors for neurocognitive sequelae after acute lymphoblastic leukemia include younger age at diagnosis, female sex, and intensity of treatment, particularly systemic high-dose methotrexate.[31] Cranial radiation was used in earlier studies of acute lymphoblastic leukemia to prevent central nervous system relapse, but effects on intelligence quotient (IQ) and academic performance have driven protocols toward chemotherapy alone.

Subjects with advanced renal failure have more often been reported, but the effects of early CKD on neurocognitive function remain incompletely elucidated. Published results from the NIH-sponsored Chronic Kidney Disease in Children Study (CKiD) have shown that IQ and academic achievement in children with mild-to-moderate CKD cluster at the lower end of the normal range, and the distribution is skewed downward.[32] Whether the severity of CKD or the duration of exposure to low GFR during brain development is of greater importance is not fully understood.

EF is the central cognitive process that controls problem-solving to permit goal-directed behavior. Various conceptual and empirical models of EF have been proposed, but most of them include the following: inhibition of prepotent responses, shifting mental sets, monitoring and regulating performance, planning and problem-solving, and working memory capacity. Control of attention is included in a construct linking EF and working memory capacity.[33–39] In addition, executive processes are considered critical to the integrity of many learning and social-behavioral functions,[35] and each of these functions has a developmental basis that will exert effects on learning and behavior at different times, with a sequential unfolding of EFs from infancy into early adulthood.[40,41] Consequently, brain injury or toxic exposure during this period of developmental ascendancy would be expected to have an effect on the integrity of EF.[42]

Several assessments of EF were incorporated into the CKiD study to determine whether EF is particularly sensitive to perturbation in a uremic milieu[43] and whether abnormalities of performance could be detected early in the course of CKD. The objective of the current study was to estimate the prevalence of EF deficits in children with mild-to-moderate CKD and to investigate what disease and patient characteristics are associated with executive dysfunction.

RESULTS

Sample description

Subjects were enrolled in the CKiD study at ages 1–16 and were followed up prospectively. The neurocognitive testing in this cross-sectional analysis was administered to 340 subjects aged 6–21 years. Characteristics of this study sample are shown in Table 1. With a median age of 13 years, the group was 61% male and 83% Caucasian, and the median parent-reported duration of CKD diagnosis was 10 years. One quarter of the study group had blood pressure measured $>$90th percentile (for age, height, and gender) on the day of cognitive testing. Because of the age of the subjects, there were no diabetics; systemic lupus erythematosus was present in only 2% and depression in 7%. Median estimated GFR (eGFR) for the group was 43 ml/min per 1.73 m^2 (interquartile range (IQR), 31–53). As reported for the entire cohort,[32] IQ clustered at the low range of normal, and 22% of the study sample had IQ scores $<$85; this was incorporated into statistical models. All subjects attended school and the

Table 1 | Characteristics of study participants ($N = 340$) at the time of first executive function testing

Characteristics	% (*n*) or median (IQR)
Age, years	13 (10,17)
Male	61% (206)
African-American	17% (57)
Maternal education	
High school or less	41% (136)
Some college	28% (91)
College or more	31% (103)
Household income	
$<$$36,000/year	38% (127)
$\geqslant$$36,000/year	62% (204)
IQ $<$ 85	22% (73)
Elevated blood pressure[a]	26% (78)
Premature birth	12% (37)
Urine protein:creatinine $\geqslant$ 2	12% (38)
Duration of CKD, years	10 (6,13)
eGFR, ml/min per 1.73 m^2	43 (31,53)
D-KEFS total achievement	10 (8,11)
Digit Span Backward	9 (7,11)
CPT-II Errors of Commission	54 (44,60)
CPT-II Hit Reaction Time	47 (40,54)
CPT-II Variability	49 (43,59)

Abbreviations: CKD, chronic kidney disease; CPT-II, Continuous Performance Test-II; D-KEFS, Delis-Kaplan Executive Function System Tower Task; eGFR, estimated glomerular filtration rate; IQ, intelligence quotient; IQR, interquartile range.
[a]Defined as systolic or diastolic blood pressure $\geqslant$90th percentile for age, sex, and height.