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REVIEW

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The nervous system and chronic kidney disease in children

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Abstract This paper provides a review of the literature on the nervous system involvement incurred by children and adolescents with chronic kidney disease (CKD), with a particular focus on neuropsychological functioning. In addition to an historical overview of earlier literature, published studies from the past 14 years that address both central and peripheral nervous system function in children with CKD are reviewed (1990–2003). These studies span work in neuroimaging, electrophysiology, and neuropsychology. A key focus for this review is on variables that might affect neurodevelopmental status in these children. The paper concludes with suggestions for achieving progress in the understanding of this complication of kidney disease in children.

Keywords Neurodevelopment · Cognition · Renal failure

Introduction

Associations between end-stage renal disease (ESRD) and neurocognitive dysfunction have been reported for over 25 years. Between 1977 and 1986, approximately 15 publications described dialysis in infants. In these early studies, approximately 65% of infants were reported to have developmental delay and 49% encephalopathy [1]. Between 1976 and 1984, the neurocognitive effects of aluminum-induced neurotoxicity secondary to then current treatments for chronic kidney disease (CKD) were reported [2, 3, 4]. These neurocognitive effects included seizures, speech disorders, dementia, and a slow electroencephalogram (EEG) pattern [2, 3]. These findings were important for the field in that they encouraged modifications to the treatment regimen for dialysis patients and highlighted a confounding factor in the relationship between CKD and neurocognitive integrity. By 1990 the use of aluminum was generally eliminated with improved dialysis water purification techniques and avoidance of aluminum-containing medications. In the early 1990s, erythropoietin was introduced into standard practice, resulting in improved anemia management for children and adults with ESRD and a diminution of anemia-related EEG and cognitive deficits reported in the adult ESRD population [5, 6, 7].

The purpose of this paper is to review the contemporary published literature that focuses on the neurological impact of CKD in children. Papers selected for this review have been published from 1990 to the present, and were selected to coincide with the improvements in treatment, including the diminution of aluminum exposure and availability of erythropoietin that occurred circa 1990. These studies span work in neuroimaging, electrophysiology, and neuropsychology to address central nervous system (CNS) function. We also present available studies addressing the integrity of the peripheral nervous system.

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Central nervous system studies

Neuroimaging

Imaging of the brain with computed tomography and magnetic resonance imaging (MRI) has been used to document the structural impact of ESRD in children.

Contemporary estimates of the prevalence of cerebral atrophy are obtained from a report of 13 children with chronic renal failure from infancy. Brain atrophy was reported in 3 (23%) of these patients [8]. Publications with a focus on certain disease groups with a high risk for CNS disease, such as cystinosis, Lowe syndrome, and congenital nephrotic syndrome, estimate the prevalence of cerebral atrophy to range between 15% and 100% [9, 10, 11]. A recent study by Qvist et al. [11] described a cohort of 33 children, largely composed of children with ESRD from congenital nephrotic syndrome, tested an average of 6 years after renal transplant. MRI documented CNS infarcts or ischemic changes from both silent and clinically significant cerebrovascular events in 19 (58%). Although relevant for children with CKD, the frequency of brain structure abnormalities in these specific disorders may be greater than in a general pediatric CKD population with a variety of renal diseases.

Electrophysiology findings

Three reports of EEG findings in a cohort of children with CKD have been published since 1990. In one study focal and paroxysmal EEG abnormalities were observed in 12 (36%) of 33 children after renal transplant, with 5 (15%) receiving anticonvulsant therapy [11]. The second report of 14 patients documented unspecified EEG abnormalities in 6 (42%) [8]. This study also documented a normal auditory brain stem evoked response in 12 of 12 children tested [8]. Hurkx et al. [12] evaluated 22 children with chronic renal insufficiency (CRI) and dialysis dependence using somatosensory evoked potential of the right median nerve. They reported an increased interpeak latency (N13–N20) suggesting a delayed thalamocortical conduction. No differences in CRI versus dialysis subgroups were found. Investigations of adults with ESRD demonstrate that these tools are sensitive to kidney disease-related effects and may prove useful in future pediatric studies [5, 6, 13].

Neuropsychology findings

Table 1 provides a brief description of 11 published studies that have been conducted over the past 15 years, with follow-up discussion on each of the studies within the broad domains of cognition listed below. These studies have employed samples ranging from 9 to 62 infants, children, and adolescents with CKD. The subjects experienced different types of treatment for their CKD (e.g., hemodialysis, peritoneal dialysis, kidney transplant, conservative). The research design varied (e.g., longitudinal, pre-post transplant, control groups) and different kinds of assessment methodology were used (e.g., infant development batteries, IQ batteries, specific measures of cognition, experimental tasks). In this regard, drawing specific conclusions for neuropsychological findings will be tentative, at best, but should provide guidance to clinicians and researchers as to how the field should move forward within this assessment domain.

General neurocognitive function

In infants and toddlers neurodevelopmental testing is conducted and analyzed in broad categories of overall development, mental development, and motor development. Hulstijn-Dirkmaat et al. [14] compared the general development in 15 toddlers receiving conservative therapy (CRI) with 16 dialysis-dependent children. The children with CRI had a better developmental index compared with the dialysis-dependent children (mean± standard deviation 90.3±14.3 vs. 67.6±17.3) [14]. Ledermann et al. [15] evaluated the long-term outcome of infants requiring peritoneal dialysis. In this study, 2 of 8 (25%) young children demonstrated developmental delay. Warady et al. [16] evaluated 28 infants at 1 year of age, all of whom were dialysis dependent. Of these 28 infants, 6 (21%) scored in the low-average or impaired range of general development. Based on these studies, approximately 20%–25% of children less than 5 years of age with CKD might be expected to show general developmental delays [8, 15, 16].

For older children, IQ is the typical measure of general cognitive function. In the sample of children studied with CKD, the 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 [11, 14, 15, 16, 17, 18, 19, 20]. In a study of 62 children with ESRD, dialysis and transplant combined, Brouhard et al. [21] described a significantly lower IQ in the children with kidney disease compared with their sibling controls. In 19 children with a mean age of 6.6±1.3 years who had ESRD from infancy, Warady et al. [16] reported a relatively intact IQ, with 15 of 19 (79%) in the average range. In this group, 13 of 18 (72%) achieved average verbal IQ scores, while only 10 (56%) scored in the average range in the nonverbal subtest [16]. When comparing transplanted patients with dialysis-dependent patients, variable results have been reported. Lawry et al. [18] compared 13 transplanted children with 11 dialysis-dependent children in a cross-sectional study and found a higher mean IQ in the transplant group (103.0±11.97 vs. 92.9±16.86). Conversely, Brouhard et al. [21] compared 36 transplant and 26 dialysis-dependent children in their cross-sectional study and found no significant difference between these patient groups. In aggregate it appears that general cognitive function is impaired in children with CKD, but the published literature is inadequate to fully characterize this effect with respect to CKD modality and differences between verbal and non-verbal IQ [11, 16, 19, 22].

Table 1 Cognitive functioning in children and adolescents with end-stage renal disease (ESRD), 1990–2003 (*CKD* chronic kidney disease, *SD* standard deviation, *CAPD* continuous ambulatory peritoneal dialysis)

Author/date	Sample features	Comparison group	Findings
Davis et al. 1990 [28]	*n*=37 20 Dialysis at pre-transplant evaluation 17 Conservative at pre-transplant evaluation Mean age at transplant=17.6 months	Pre-post transplant design	Mental development Improved from pre- (mean=77.0, range 50–116) to post-transplant (mean=91.4, range 50–117) Motor development Improved from pre- (mean=68.7, range 50–86) to post-transplant (mean=85.6, range 65–109) Cognition No change from pre- (mean=92.0) to post-transplant (mean=90.4) Overall development worse with early onset of ESRD
Fennell et al. 1990 [22]	*n*=56 Mean age=13.6 years Mean age of CKD onset=6.05 years Modality: Hemodialysis (7) Peritoneal dialysis (12) Kidney transplant (10) Conservative (27)	*n*=56 healthy children Testing at 6-month intervals	Cognition Decreased verbal ability in CKD Visual motor skills Decreased in CKD Memory and learning Decreased in CKD Loss of function over time Attention No differences between CKD and controls
Lawry et al. 1994 [18]	*n*=24 Modality: Dialysis (9) Conservative (2) Kidney transplant (13)	Transplant compared with dialysis plus conservative	Cognition IQ: no differences between dialysis plus conservative (mean=92.91, SD=16.86) vs. transplant (mean=103.00, SD=11.97) Correlation between age at onset of illness and IQ (r=0.49) Achievement Dialysis plus conservative less than transplant in maths (P=0.020), reading (P=0.028), and written language (P=0.028)
Elzouki et al. 1994 [8]	N=15 Modality: Dialysis (6) Transplant (3) Conservative (6)	None	Developmental screening 3 of 15 with developmental delay
Hulstijn-Dirkmaat et al. 1995 [14]	*n*=31 Mean age=2.5 years Modality: Dialysis (16) Conservative (15)	None Testing every 6 months	Developmental index Conservative (mean=90.3, SD=14.3) greater than ESRD (mean=67.6, SD=17.3) Verbal, perceptual performance, and quantitative scales No change over time
Mendley and Zelko 1999 [19]	*n*=9 Mean age at pre-transplant testing=14.2 years Mean age at post-transplant testing=15.8 years Pre-transplant modality: Peritoneal dialysis (5) Hemodialysis (3) Conservative (1) Mean age of onset of ESRD=11.9 years Mean duration of ESRD prior to transplant=2.5 years	Pre-post transplant design	Cognition (baseline only) Full-scale IQ mean=91.6 Verbal IQ mean=91.4 Performance IQ mean=95.1 Attention Improvement in sustained attention 1-year post-transplant (P=0.039) Executive functioning Improvement in mental processing speed 1 year post transplant (P=0.008) Memory Improvement in working memory 1 year post transplant (P=0.016)
Warady et al. 1999 [16]	*n*=28 infants Modality: CAPD at $\leq$3 months of age Transplant at mean age=2.1±0.8 years Mean age at follow-up=7.8±2.8 years (range 2.5–12.0 years)	Longitudinal design	Development, general 6 of 28 children below the average range at 1 year of age Cognition Verbal IQ: 5 of 18 children below the average range at $\geq$4 years of age Non-verbal IQ: 8 of 18 children below the average range at $\geq$4 years of age 1 child within impaired range on both verbal and non-verbal IQ

Table 1 (continued)

Author/date	Sample features	Comparison group	Findings
Ledermann et al. 2000 [15], Madden et al. 2003 [17]	*n*=16 infants with ESRD Mean age at start of dialysis= 0.38 years (range 0.02–1 year) Duration of dialysis=17.3 months (range=1–59 months) Mean age at assessment=5.84 (range 1.58–12.00 years)	Longitudinal design	Development, general 2 of 8 school-aged children had general delays 2 of 8 children <5 years of age had general delays Cognition IQ: 67% in average range, and 20% in low-average range (mean=86.5, range 50–102) Lower IQ scores for children with co-morbid diagnoses (mean=67.0) than for those with ESRD alone (mean=94.2) Attention 7 of 14 children with hyperactivity problems Social-behavioral 6 of 14 children displaying conduct problems
Brouhard et al. 2000 [21]	*n*=62 Mean age: 13.8±0.4 years Modality: 26 dialysis, 36 transplant	*n*=62 siblings	Cognition IQ: ESRD less than siblings No difference in dialysis vs. transplant Academic achievement ESRD less than controls for all measures of spelling, reading, and mathematics No difference dialysis vs. transplant Correlation between age of diagnosis and academic achievement Correlation between parental education and academic achievement
Qvist et al. 2002 [11]	*n*=33 transplant recipients Mean age at assessment=8 years (range=7–12 years)	None	Cognition Verbal IQ: mean=87.5 Non-verbal IQ: mean=87.5 IQ range Low: 3/33 Low-average: 14/33 Average: 14/33 Above average: 2/33 Neuropsychological battery No overall group deficits with attention, language, memory, or visuospatial abilities when compared with normative population Neuropsychological deficits Attention: 8 of 33 children Language: 2 of 33 children Memory: 6 of 33 children Visuospatial: 8 of 33 children Motor function Hemiplegia: 3 of 33 children Bilateral infarction: 1 of 33 Cerebral palsy: 1 of 33 Auditory function 2 of 33 children with moderate sensorineural hearing loss

Attention and executive function

The findings in the pediatric CKD literature are mixed with respect to attention and executive function [11, 19, 22]. Fennell et al. [22] reported no differences in measures of sustained attention between children with all treatment modalities of CKD combined and matched controls. Conversely, Mendley and Zelko [19] documented longitudinal improvements in sustained attention (pre-transplant 2.19±1.29 vs. post-transplant 2.95±1.33, P=0.04) and mental processing speed (pre-transplant 2.28±0.72 vs. post-transplant 1.64±0.31 s, P=0.008) 1 year after transplant in 9 children. After renal transplant, Qvist et al. [11] reported no overall group deficits of attention in 33 children compared with the normative population [standard deviation score (SDS)=–0.2±0.4], although 24% of the sample showed generalized attention deficits.

Language

The prevalence of hearing loss among children with CKD is approximately 18%, and unrecognized or delayed diagnosis of hearing impairment may impede language development [11, 23]. Children with known hearing loss

tend to be excluded from studies of cognitive function, and so their challenges are not likely to be fully reflected in the published literature [17]. Fennell et al. [22] documented deficits with verbal abstracting abilities in their matched control design for children with CKD. Qvist et al. [11] documented no overall group deficits of language compared with the normative population (SDS=–0.2± 0.4), with only 6% of children showing evidence of generalized language deficits. More research needs to be conducted before determining whether language abilities will prove to be an area of concern for children with CKD, particularly with respect to potential delays secondary to hearing impairment.

Visuospatial abilities

Compared with a matched control population, early studies by Fennell et al. [22] documented deficits in visual-motor abilities in a cohort of 56 children with CKD. Qvist et al. [11] documented no overall group deficits with visuospatial abilities in 33 transplant recipients when compared with the normative population (*SDS*=–0.5± 0.5); however, 24% of the cases did show generalized visuospatial deficits.

Memory

In a heterogeneous sample of children with CKD, Fennell et al. [22] reported lower memory scores for children with CKD compared with controls. In addition, a general loss of memory function over time was observed in 26 children with all treatment modalities of CKD over a 12-month testing period [24]. After kidney transplantation, Qvist et al. [11] reported no overall group deficits with memory compared with the normative population (SDS=–0.4±0.5), although 20% of the cases displayed generalized memory deficits. Conversely, Mendley and Zelko [19] documented longitudinal improvements in working memory in 9 children 1 year after transplant compared with the pre-transplant evaluation.

Academic achievement

Academic achievement in children with CKD is vulnerable to deficits in each cognitive domain noted above as well as an increased frequency of school absences. In a study by Lawry et al. [18], the combined dialysis and CRI group (n=11) with a mean chronological age of 14.9±3.3 years achieved at an age equivalent of 13.8±5.8 in mathematics, 15.6±7.7 in reading, and 11.2±7.2 in language. In comparison, the transplant group (n=13) with a mean chronological age of 13.8±3.2 years, achieved at an age equivalent of 16.2±7.8 in mathematics, 16.4±7.7 in reading, and 16.2±9.1 in language. This paper suggested that transplant recipients may have superior academic achievement compared with dialysis-dependent children [18]. Conversely, Brouhard et al. [21] compared the academic achievement of dialysis and transplant patients and normal sibling controls. They reported no difference in academic achievement between dialysis and transplant groups. However, the combined ESRD group of dialysis and transplant achieved below their sibling controls in spelling, arithmetic, and reading [21]. Observational studies of academic placement further indicate that regular education (with or without remedial tutoring) is used for 79%–94% of children with CKD, while 13%–15% receive special education services not related to hearing or visual impairments [11, 16]. This compares with national data in which approximately 10%–15% of students receive special education services [25]. Given the observed frequency of abnormalities across multiple areas of cognitive function, the frequency of special education services used by children with CKD appears low.

Peripheral nervous system

Peripheral neuropathy including diabetic neuropathy and dialysis-related amyloidosis has been reported in adults with ESRD [26, 27]. The frequency of peripheral neuropathy in children with CKD can only be grossly estimated based on the following study. Elzouki et al. [8] assessed nerve conduction velocity in 11 children with CKD and found 1 (9%) had diminished motor nerve conduction. Electromyograms performed in 9 of these patients revealed increased polyphagia of motor unit potentials in 4 (44%) [8]. At present, we are unable to find additional published studies examining peripheral neuropathies in children with CKD.

Key variables affecting neurodevelopmental outcomes

CKD is a complex disorder and, similar to other pediatric disorders, there are undoubtedly a variety of variables that contribute to the neurodevelopmental status of this population. Key variables presented here are postulates for the most part as the studies conducted since 1990 have not been adequately powered to assess multiple influential factors.

The duration of CKD and the age at onset of CKD may affect cognition. Two separate studies have reported a poorer developmental prognosis for children with earlier-onset ESRD [18, 28]. It has been postulated that this may be the result of insults to the CNS at particularly vulnerable periods in development or the result of continuous insults over the majority of postnatal life among some children with long-standing kidney disease. The congenital disorders presenting with kidney disease early in life may influence the perceived relationship between duration of CKD and cognition, as these disorders may have other associated CNS abnormalities, such as pulmonary hypoplasia and hypoxia associated with obstructive uropathies, or structural anomalies with Joubert syndrome

and Smith-Lemli-Opitz syndrome [29]. Hulstijn-Dirkmaat et al. [14] identified the presence of co-morbid conditions as a risk factor for cognitive impairment based on mean IQ scored (CKD alone 86.7 vs. CKD with co-morbidity 61.4, P=0.001). Conversely, Fennell et al. [24] found no correlation between age at onset of ESRD and cognition. The available data suggest that the duration of CKD and the age at onset of CKD negatively impact on cognitive functioning, but it remains unclear how these variables contribute to the type and severity of cognitive dysfunction.

Having reached ESRD, the modality of renal replacement therapy may have an impact on neurodevelopment. Several studies have examined small groups of children either before and after renal transplant or as a cross-sectional study comparing renal replacement therapy modality groups [30, 31]. Fennell et al. [24] compared 10 transplant, 7 hemodialysis, and 12 peritoneal dialysis patients. Patients in both the transplant and peritoneal dialysis groups tended to have better attention and memory skills when compared with the performance of hemodialysis patients. Additional investigation is warranted to determine the differential effect of hemodialysis and peritoneal dialysis among children with ESRD with current dialysis adequacy standards [32, 33, 34]. From previous studies, a hypothesis can be formulated that motor skills, memory, attention, and mental processing may improve after renal transplantation [11, 16, 21]. Although existing literature suggests that a successful renal transplant may diminish the adverse developmental effects of ESRD, these same studies document the type and frequency of residual deficits in pediatric renal transplant recipients to be greater than in the normative American population [11, 16, 21].

Complications of CKD such as anemia, hypertension, and malnutrition likely affect neurodevelopment. 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 [6, 35]. The optimal hemoglobin for cognitive function in children with CKD remains to be determined. The effects of hypertension on cognition may be related to the degree of blood pressure elevation, brain injury consequent to hypertensive or hypotensive episodes, and side effects of antihypertensive therapy. A recent study by Lande et al. [36] analyzed National Health and Nutrition Examination Survey III (NHANES III) data comparing 217 children with systolic blood pressure greater than or equal to the 90th percentile for age and gender with 4,860 normotensive children. The NHANES III study used subtests of the Wechsler Intelligence Scale for Children and reading and arithmetic subtests of a standardized academic achievement test. In this study, results suggested that hypertension was associated with lower scores in subtests representing memory, attention, and arithmetic. Furthermore, malnutrition in young infants without kidney or other chronic disease has been linked to impaired brain growth and developmental delay [37, 38, 39]. Significant effort has been applied to the nutritional support of children with CKD. However, in national registries of children with CKD, the mean weight z-score is 1.0–1.4 standard deviations below the American age-matched mean, and mean height z-scores are approximately 1.6 standard deviations below the American age-matched mean [40]. Anemia, hypertension, and malnutrition are likely key factors contributing to the cognitive deficits of children with CKD.

Children with CKD are at risk for additional disorders that may accompany congenital kidney disease. Prematurity occurs with a greater frequency in children with congenital kidney disease and is associated with a greater frequency of CNS injuries and later developmental deficits [11, 41]. Socioeconomic status and parental education have a known impact on academic achievement among all children [42]. Although not unique to children with CKD, the identification of poor socioeconomic status or limited parental education may trigger additional educational evaluation and or services for children with CKD in these families. School absences are increased in children with CKD due to the need for outpatient medical visits, hospitalizations, hemodialysis, and acute illness [20]. Finally, the CKD population is at excess risk for sensory deficits, including congenital and acquired hearing impairment (9%-18%) and visual impairment, although the latter has not been examined thoroughly [11, 43]. All of these factors may contribute to the neurodevelopmental dysfunction of children with kidney disease.

Conclusions

Emergent findings appear to apply to three broad groups of children and adolescents: mild-to-moderate CKD, dialysis-dependent children, and transplant-dependent children. What is known about children with mild-to-moderate CKD is severely limited, with no focused studies addressing their neurodevelopmental needs. More is known about the pediatric dialysis population, with deficits in the areas of attention, language, visual-spatial abilities, and memory. However, the differentiation of problems that may relate to disease-specific variables, such as age at onset of kidney failure, anemia, and hypertension, remain relatively unknown and modestly examined at best. For the transplant-dependent group, cognitive deficits appear to persist, supporting the conclusion that the transplant does not result in complete neurocognitive "recovery."

The low frequency of peripheral neuropathy in children with CKD observed clinically and reported in a single study may be attributed to the low prevalence of diseases with microvascular complications such as diabetes mellitus, advanced atherosclerosis, and dialysis-related amyloidosis [8]. This pediatric advantage may be lost as patients survive into young adulthood. It is unlikely that purely pediatric follow-up studies will be able to characterize this potential late-term complication.

Given the expected long-term patient survival of children with CKD, established guidelines for the provi-

sion of renal replacement therapy for children, and the data provided by studies among children with CKD, we believe that an organized, adequately powered approach toward the characterization of the neurodevelopmental impact of CKD is warranted [32, 33, 34, 44]. Ideally, this study or set of studies will include measures of neuroimaging, electrophysiology, and neuropsychology. Future research in this area should characterize potential risk factors, such as age at onset of disease, anemia management, and hypertension to advance our understanding of the magnitude of cognitive dysfunction and aid the identification of modifiable mediators of CNS deficits in children with CKD.

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