Neurocognitive Functioning in Pediatric Dialysis

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Introduction

Children and adult survivors of childhood-onset chronic kidney disease (CKD) have a greater frequency of neurodevelopmental and cognitive challenges compared with the general population [1, 2]. The impact of this neurodevelopmental vulnerability persists into adulthood and contributes to clinical manifestations such as a lower intelligence quotient and a lower frequency of postsecondary education compared with the general population [2]. The mechanisms responsible for the brain dysfunction observed with CKD have not been established, although a number of mechanisms have been hypothesized and are discussed below. The goals of this chapter are to explore potential mechanisms leading to brain dysfunction—including renal-brain connections—summarize known neurocognitive and neurologic findings, and consider possible management strategies for neurocognitive dysfunction in children affected by CKD, particularly once they reach end-stage kidney disease (ESKD).

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The Interaction of Brain Development, Kidney Disease, and Dialysis

Brain Development

Brain development is quite rapid during early childhood and, subtler but equally as critical, in later childhood and adolescence. Consequently, expectations for developmental attainment and general cognitive performance change as the child ages. The timing of this rapid neurodevelopmental growth places the developing brain at particular risk from injury or disease during infancy and childhood. Dennis et al. [3] and others [4] have suggested that the degree and severity of insult is likely related to when the insult occurs in the neurodevelopmental sequence and the cognitive reserve of the individual. Studies of other childhood chronic health conditions present from birth or shortly thereafter have found delays in language, motor skills, and overall developmental level [5–8]. In addition, children with early traumatic brain injury have shown deficits in academic achievement, behavior, cognitive, and motor functioning at the time of injury [9, 10], and these deficits persist long past the initial insult [11]. Given the rapid rate of this early neurodevelopmental growth, these deficits may be worse than brain insults obtained in later years [12]. Although there are relatively few studies of the longitudinal impact of CKD in infancy and early childhood, several studies suggest an

increased risk of developmental delays in children with early-onset chronic kidney disease (CKD) or end-stage kidney disease (ESKD) [13–15] and in children with a longer duration of CKD or dialysis [16–19]. Further research is needed to improve our understanding of how CKD affects the developing brain and how factors such as age of onset, prematurity, disease severity, duration of disease, and treatment modality moderate immediate and downstream neurocognitive outcomes.

Kidney-Brain Connections

Given the above findings from the available pediatric neurocognitive and neurological literature, there is a clear connection between the kidney and brain. These observations generate key questions: How does kidney dysfunction contribute to brain dysfunction or damage? What do we know about possible mechanisms and how can they affect brain structure, brain function, and brain development?

Potential mechanisms of neurocognitive impairment in CKD include metabolic neuronal toxicity, vascular injury, and endothelial dysfunction, all of which are likely interrelated. At its simplest level, CKD may impact the nervous system by not effectively filtering neurotoxic chemicals and metabolites from the bloodstream, leading to metabolic neuronal injury. This mechanism may be most evident when the individual reaches end-stage kidney disease. Alterations in vascular integrity also may be present secondary to the metabolic changes associated with CKD as well as by its comorbidities such as hypertension, anemia, and dyslipidemia. Vascular injury may be further perpetuated by endothelial dysfunction, mediated by chronic inflammation, hypercoagulability, and oxidative stress [20].

In addition to the potential direct effects of kidney dysfunction on the brain, medical management of CKD and ESKD may affect neurocognitive outcomes. Factors such as malnutrition, aluminum intoxication, and psychosocial deprivation have historically contributed to adverse neurocognitive outcomes in children with CKD [21]. More

modern treatment protocols may help to mitigate these effects by optimizing nutrition, reducing aluminum exposure by eliminating aluminum-containing phosphate binders and optimizing dialysis water treatment, and paying greater and more consistent attention to children's cognitive, educational, and psychosocial needs during medical treatment. Similarly, improved management of anemia in children with ESKD may also buffer the impact of CKD on the nervous system based, in part, on findings in adults with ESKD [22]. Dialysis itself may also contribute to neurocognitive dysfunction in the long term, as discussed further in the next section.

Metabolic Changes in CKD CKD causes retention of a large number of uremic toxins that differ in their molecular weight, protein binding, and ability to be removed by dialysis [23]. Many of these uremic toxins have known or putative roles in cerebral dysfunction. For example, guanidino compounds, which are known to have pro-convulsant properties [24, 25], have been found in elevated levels in the serum, urine, cerebrospinal fluid, and brain tissue of patients with CKD [26–28]. Another pathway known to be altered in CKD is the kynurenine pathway of tryptophan metabolism, which is also implicated in the pathogenesis of various cognitive and neurodegenerative disorders independent of CKD [29]. In one study of adults with stage 4 CKD, higher serum levels of kynurenic acid were associated with lower cognitive functioning, while higher serum levels of indole-3 acetic acid (IAA) were correlated with anxiety and depression [30].

The advent of metabolomic profiling, in which hundreds of compounds can be measured in a single sample, may help to broaden our understanding of the numerous metabolic changes associated with CKD and their relationship to neurocognitive function. In one study of adults on maintenance hemodialysis, metabolic profiling of pre-dialysis plasma samples showed that levels of four metabolites related to phenylalanine, benzoate, and glutamate metabolism were associated with impaired executive function [31].

Imaging methods, such as magnetic resonance spectroscopy (MRS), may also help to deepen our understanding of the relationship between metabolic changes and neurocognitive dysfunction in CKD. For example, in one study of children with stage 1–5 CKD, including children on dialysis, MRS of the brain showed that the intelligence quotient (IQ) correlated negatively with the brain myoinositol/creatine ratio and positively with the N-acetyl aspartate (NAA)/creatine ratio [32]—neurometabolites related to neurotransmission and tissue damage or necrosis, respectively.

Some studies of the effects of dialysis and transplant on neurocognition also support the hypothesis that metabolic changes are at least partially responsible for neurocognitive dysfunction in CKD. In one small study, an electrophysiologic measure of cognitive potential, the P300 latency, was found to be impaired in adults with ESKD and also was found to normalize 3 months after successful kidney transplantation, presumably due to normalization of metabolic processes [33]. In another pilot study, transition of patients from conventional dialysis to nocturnal daily hemodialysis, which improves clearance of uremic toxins, was associated with improved psychomotor efficiency, attention, and working memory [34].

Vascular Integrity Another potentially strong linkage between kidney disease and brain impairment relates to the vascular integrity in both of these organs. Indeed, there are a number of similarities in the vascular supply to both the brain and kidney, with both being low-resistance end organs that manage high volumes of blood flow. Murray [35] and others have argued for a linkage between the kidney and the brain that is based on a model of accelerated vascular cognitive impairment.

Adults with CKD and ESKD are at much higher risk for cerebrovascular complications than the general population. In the 2006 United States Renal Data System Annual Report, the incidence of stroke was 15.1% in hemodialysis patients and 9.6% in CKD patients, compared to only 2.6% in non-CKD Medicare patients [36]. Preliminary evidence also has begun to show sig-

nificantly higher rates of stroke, even in children with mild to moderate CKD [37]. Although coexisting risk factors, such as hypertension, diabetes, and dyslipidemia, contribute to stroke risk in many adults with CKD, having a glomerular filtration rate (GFR) of <60 mL/min/1.73m^2 has been shown to be independently associated with an increased risk of stroke [38]. Even in adults with CKD, but without a known clinical history of stroke or transient ischemic attacks, magnetic resonance imaging (MRI) studies have revealed a high prevalence of cerebrovascular abnormalities. In a study of more than 1000 adults, Liu et al. [39] found that GFR <60 mL/min/1.73m^2 was associated with an increased prevalence of markers of cerebral small vessel disease (e.g., lacunes, white matter hyperintensities, cerebral microbleeds, enlarged perivascular space) in individuals <60 years old, even after adjustment for comorbidities such as hypertension and diabetes. In nondiabetic adults, aged 30–60 years, with stage 3–4 CKD, Martinez-Vea et al. [40] found that 1/3 had silent cerebral white matter lesions, with vascular nephropathy being the strongest independent risk factor for the presence of these lesions. Similarly, Kobayashi et al. [41] found a high prevalence of silent brain infarction (SBI) in adults with CKD, with hypertensive nephrosclerosis showing a strong association with SBI.

Although the pediatric data are more limited, MRI studies in children with CKD also show evidence of alterations in cerebral vascular integrity. Among children who received a kidney transplant before 5 years of age, Valanne et al. [42] showed a 54% prevalence of ischemic lesions in vascular border zones. Although overt MRI lesions are much less common in children and young adults with milder CKD [43], a study of cerebral blood flow (CBF) using arterial spin-labeled (ASL) MRI showed that individuals aged 8–25 years with CKD had higher global CBF than healthy controls (primarily related to anemia). In addition, white matter CBF was positively correlated with blood pressure in CKD patients but not in healthy controls, suggesting abnormal cerebrovascular autoregulation in individuals with CKD [44]. This study also showed

that regional differences of CBF in the precuneus correlated with executive dysfunction. These findings provide some early mechanistic insights into how hypertension, a known risk factor for decreased neurocognitive performance in children both without [45] and with CKD [46, 47], may contribute to neurocognitive dysfunction.

Other factors that may contribute to impaired cerebral vascular integrity and cognitive impairment include hyperhomocysteinemia, oxidative stress, and inflammation. Hyperhomocysteinemia is common in patients with CKD [48] and may contribute to neurocognitive dysfunction both via endothelial pro-inflammatory effects and via its direct effects on the N-methyl-D-aspartate receptor [49, 50]. Oxidative stress, mediated by alterations in endothelial nitric oxide signaling, also has been linked to brain dysfunction in adults with CKD and in experimental models [51, 52].

The Impact of Dialysis on Kidney-Brain Connections

Chronic Dialysis Although clearance of uremic toxins by dialysis may improve neurocognitive function, chronic dialysis is associated with physiologic changes that may negatively impact brain function. In adults, initiation of hemodialysis (HD) is associated with a higher incidence of dementia-related symptoms when compared to patients initiating peritoneal dialysis (PD), even after adjustment for comorbidities and controlling for factors that influence dialysis modality selection [53]. In a longitudinal study, cognitive function declined faster in adults on dialysis compared to those with CKD, and the decline was faster in patients on HD than patients on PD [54]. Factors contributing to cerebral dysfunction in dialysis may include repeated episodes of cerebral hypoperfusion caused by hypotension and fluid shifts, which can lead to increased risk of brain ischemia and watershed infarcts. In a study using positron emission tomography-computed tomography (PET-CT) in older adults on hemodialysis, global CBF was found to decline significantly during HD (mean decline of $10 \pm 15\%$), and the degree of CBF decline was associated with higher ultrafiltration (UF) volume and UF rate [55]. Although HD is associated with greater degrees of hemodynamic changes compared to PD, the risk of stroke has been shown to increase in older adults within 30 days of initiating either dialysis modality [56], suggesting that cerebral hypoperfusion can occur with both HD and PD.

Even in stable chronic dialysis patients, HD has been shown to be associated with short-term changes in cognitive performance. In studies of adult patients receiving HD, Costa et al. [57] and Dasgupta et al. [58] demonstrated deterioration of cognitive function when comparing performance before HD versus immediately after HD. Murray et al. [59] showed that global cognitive function in adults varies during a dialysis cycle, with worse performance during the HD session and best performance either shortly before or on the day after the session.

As discussed in more detail in the next sections, multiple studies in children receiving chronic dialysis have shown impaired neurocognitive performance in various domains [60–68]. However, there is very little literature examining the extent to which dialysis-related physiologic changes contribute to neurocognitive impairment in children. In their study of children who received a kidney transplant before age 5 years, Valanne et al. [42] described three patients who had marked widening of the cortical and central cerebrospinal fluid spaces on CT scans performed while receiving chronic dialysis; importantly, it was reported that these abnormalities resolved on posttransplant MRI (Fig. 34.1). They postulated that this reversible "pseudoatrophy" was a result of reversible contraction of brain tissue caused by factors such as fluid/electrolyte shifts, hypoalbuminemia, or medications [42]. However, more definitive physiologic studies of the effects of dialysis on the pediatric brain are needed.

Acute Dialysis Dialysis disequilibrium syndrome can arise acutely during or immediately after a dialysis session, most commonly in patients receiving their first HD treatment [69]. Symptoms of dialysis disequilibrium can include headache,
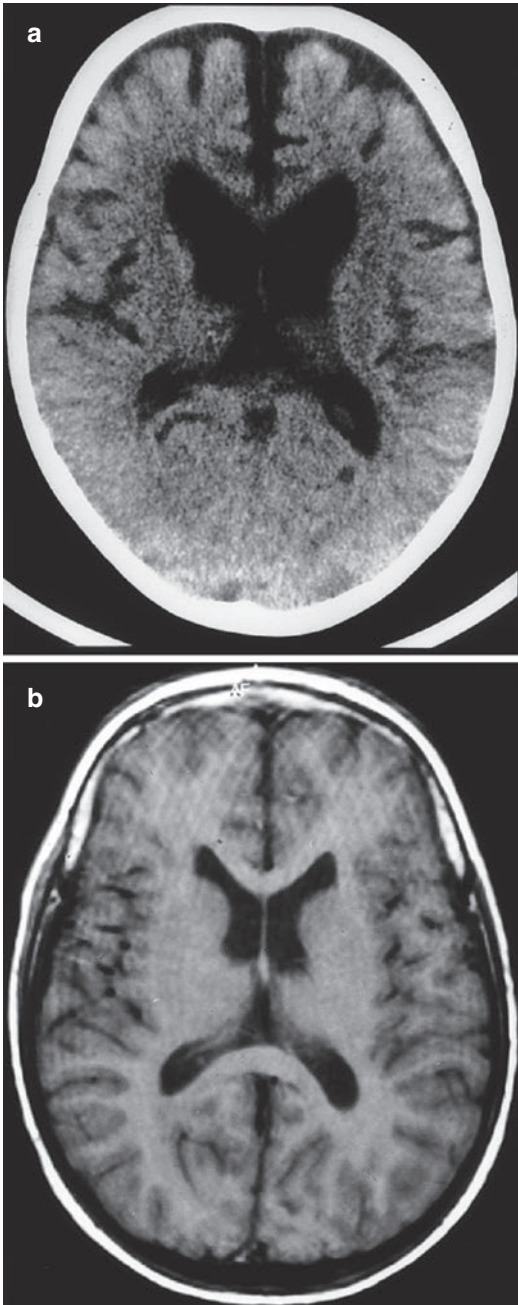
Fig. 34.1 This CT scan presents reversible "pseudoatrophy" in a patient on dialysis. (**a**) shows the presence of larger and misshapen lateral ventricles as well as widening of the subarachnoid spaces in frontal brain regions during dialysis. (**b**) shows an apparent resolution of these abnormalities in the same patient several years posttransplant. (Reprinted with permission from Wiley & Sons)

confusion, nausea, restlessness, and coma. These symptoms are primarily related to cerebral edema and increased intracranial pressure caused by osmotic movement of water into the brain.

There are two hypotheses for the mechanisms responsible for an osmotic gradient between the blood and the brain, namely, the "reverse urea" hypothesis and the "idiogenic osmoles" hypothesis [70]. The "reverse urea" effect is thought to occur because rapid removal of blood urea by dialysis leads to a blood-brain urea gradient, causing osmotic movement of water into the brain [71]. The "idiogenic osmoles" hypothesis arose from animal experiments in which rapid HD was associated with significantly higher brain tissue osmolality compared to the blood, which could not be fully explained by changes in electrolyte or urea concentrations [72]. This led the authors to conclude that the increased brain osmolality was caused by the new formation of organic molecules; however, a subsequent study of rapid HD in another animal model could not confirm the presence of "idiogenic osmoles" [73].

Regardless of the underlying mechanism, the primary method to prevent dialysis disequilibrium is to lower the blood urea concentration slowly, either via slow continuous HD or hemofiltration or by targeting lower urea reduction ratios [69]. Another approach to mitigate dialysis disequilibrium, and perhaps associated neurocognitive impairment, includes increasing blood osmolality by increasing dialysate sodium concentration [74] or by infusing mannitol [75].

Neurocognitive Functioning and Neuroimaging in Pediatric Dialysis

Neurocognitive Functioning in Pediatric Dialysis

Over the past 5 decades, the cognitive function of small cohorts of children receiving various forms of renal replacement therapy (RRT) has

been evaluated. Although informative, results from investigations conducted prior to 1990 were likely significantly influenced by uncontrolled anemia, aluminum exposure, and potentially less stringent nutritional, dialytic, and transplantation services compared with present-day management. Despite the improvement in these treatments [76], even more contemporary findings continue to be plagued by small sample sizes, samples that combined multiple forms of treatments and associated treatment protocols without differentiation, and samples that combine patients with wide age ranges. Further, there is little consistency across the neurocognitive measures used so as to compare one study to the next. These are not research oversights by investigators in the dialysis literature, but rather the result of the challenges of subject ascertainment and the medical needs of the children. A summary of the findings from the available contemporary studies over the past three decades is provided in Table 34.1.

Early studies and overviews of the CKD literature indicated significant concerns for several developmental delays—including gross motor and language functions and other neurological problems (e.g., microcephaly) in both dialyzed and non-dialyzed infants with severe CKD and ESKD [79, 80]. As can be seen in Table 34.1, infants and very young children on dialysis show developmental delays and significantly lower IQ scores compared to healthy children [60–64]. With respect to overall developmental functioning, many children on dialysis have been reported to be in the intellectual disability range. For older children and adolescents, a similar pattern of findings has been present, with overall intellectual functioning being approximately 9–11 points lower than controls [65]. Further, older children and adolescents also have had evidence of poorer abilities in their gross motor, fine-motor coordination, visuomotor skills, short-term memory, verbal abilities, and attention [66–68, 81]. More specifically, memory impairments are particularly noteworthy relative to the healthy control populations, and this impairment is greatest with dialysis-dependent ESKD [68].

A variety of executive function problems also have been reported, with particular concerns noted for problems in working memory, initiation, and sustaining capabilities [68]. Significant problems also have been reported in academic achievement across reading, spelling, and math areas, increased school absences, more frequent grade retentions, and the presence of formal learning disabilities [82, 83]. Unfortunately, we have a paucity of information regarding the impact of CKD and dialysis on specific language functions, overall motor skills, and adaptive behavior in children.

In contrast, several studies have not uncovered significant differences between children with ESKD and controls in the areas of memory, selected executive functions, academic achievement, or self-assessment of health-related quality of life [65, 66, 68, 84]. Furthermore, follow-up studies of children who have received kidney transplants, typically following some time on dialysis, generally have shown relative improvements in overall cognitive functioning. For instance, attention appears to be most severely affected with dialysis-dependent ESKD but reportedly improves after transplantation [15, 21, 81]. Qvist et al. [85] reported low average to average IQ in school-age children who received transplants before age 5 years, with as many as a quarter of the children continuing to show some type of neurocognitive impairment several years posttransplant. Improvements in both verbal and nonverbal IQ have been consistently reported following kidney transplantation [60, 86–88], with about a 10–12-point improvement in IQ being demonstrated at least one month or more posttransplant. Significant improvements also have been observed in processing speed, reaction time, and working memory [81]. Nevertheless, having ESKD in childhood does not appear to bode well for individuals as they move into older childhood or adulthood, with findings suggesting lower verbal and nonverbal intellectual capacities [2], lower academic achievement, and the presence of metacognitive executive dysfunctions [15]. Shorter duration of dialysis in childhood and older age at the time of renal replacement therapies—including transplant—also have been related to better outcomes [2, 15, 89].

Table 34.1 Summary of neurocognitive outcome studies in children and adolescents with ESKD and/or receiving renal replacement therapy

Study	Study population	Neurocognitive outcomes
Davis et al. (1990)	37 children, 25 males and 12 females, undergoing primary transplant evaluation; 20 on dialysis at pretransplant evaluation; 17 with conservative management; mean age at transplant was 17.6 months	Bayley Mental Developmental Index mean was 77 at pretransplant and 91 at posttransplant. Bayley Psychomotor Developmental Index was about 69 at pretransplant and about 86 at posttransplant. Early transplant improved both motor and cognitive developmental status in infants
Fennell et al. (1990)	56 children with CKD; 29 receiving dialysis or transplant and 27 receiving conservative management; 56 age-, race-, and gender-matched health controls; average age = 13.4 yrs	Patients with CKD performed more poorly than controls on visuomotor skills, short-term memory, and verbal abilities. No differences between groups on measures of attention. No differentiation of different types of renal replacement therapies
Lawry et al. (1994)	24 children with CKD, 9 receiving dialysis, 13 receiving transplant, and 2 CKD	Patients receiving transplant performed better on academic achievement tests of written language. They also showed better school performance in English compared to dialysis patients
Hulstijn-Dirkmaat et al. (1995)	31 children, 18 males and 13 females; mean age = 2.5 yrs; 16 receiving HD and 15 CKD	The overall sample was delayed when compared to normal expectations with a Bayley Index of 78.5. Those receiving HD performed evenly more poorly when compared to the CKD group, with scores reflecting intellectual disabilities (Bayley mean = 67.6)
Mendley and Zelko (1999)	9 children, 5 males and 4 females; 5 were receiving PD, 3 HD, and 1 conservative treatment; mean age at pretransplant was 14.2 yrs	Transplant patients significantly improved in reaction time, working memory, and attention posttransplant
Warady et al. (1999)	28 children who started PD < 3 months of age; 24 received transplant at about 2.1 yrs. of age	At 1 year of age, 79% were in average range on developmental testing; 4% were in the below average range of development. At approximately 4 yrs. of age, the percentages remained stable. At approximately 5 yrs. of age, nearly all children were attending school full time and in age-designated classrooms
Ledermann et al. (2000)	20 infants, ranging from birth to 12 months, in long-term peritoneal dialysis	Small head circumference approaching microcephaly, with increased head growth over time. There were 16 survivors, with 14 showing normal development post RRT
Brouhard et al. (2000)	124 subjects: 62 ESRD subjects on dialysis (26) or transplant (36) and 62 sibling controls; mean age was 13.8 yrs	Patients with ESRD performed significantly lower than controls on IQ, academic achievement (reading, spelling, and math). Increased time on dialysis was associated with lower scores
Crocker et al. (2002)	4 children with congenital ($n = 13$) or acquired ($n = 11$) ESRD; 15 dialysis and 9 CKD; no CNS syndromes and no suspected CNS medication effects	Neuropsychological testing showed no group differences in IQ, academic achievement, or short-term memory. The congenital ESRD group performed significantly worse on tasks of fine-motor coordination, long-term memory
Bawden et al. (2004)	44 children, 22 on dialysis or awaiting transplant and 22 sibling controls	Children with ESRD exhibited lower IQs of approximately 9–11 points across both verbal and nonverbal abilities than their sibling controls. Significant differences also were noted in fine-motor coordination and visuoconstructive abilities; however, the groups were commensurate in their academic achievement, memory, ratings of behavior, and self-esteem. Overall neurocognitive functioning was deemed more favorable than expected for children with ESRD

(continued)

Table 34.1 (continued)

Study	Study population	Neurocognitive outcomes
Eijsermans et al. (2004)	10 children, 8 males and 2 females, with chronic renal failure with HD for at least 1 month; mean age = 12.3 yrs	Presence of significant gross motor problems in the majority of children on dialysis, with only 1 participant showing fine-motor problems. No concerns were noted in self-assessments of health-related quality of life
Gipson et al. (2006)	20 children with CKD, ages 7.5–19 yrs. (Mean = 13.4), with 12 receiving dialysis and 8 conservative therapy; 18 healthy controls	Intellectual function for the CKD group was within the low average to average range ($M = 89.32$) and significantly lower than the controls ($M = 112.18$). After controlling for IQ, the CKD group performed significantly lower than the controls on all memory functions. The CKD group also was significantly lower on some executive functions (initiation, sustaining) but performed similarly to controls on other executive functions (inhibition, set shifting)
Duquette et al. (2007)	30 children with CKD, including 15 receiving dialysis; 41 healthy controls	Compared to healthy controls, children with CKD experienced more grade retentions, school absences, and lower achievement skills in math and reading. They also satisfied criteria for a low achievement definition of learning disabilities more so than the controls

Note. Table adapted from Moodalbail and Hooper [77] and Gipson and Hooper [78]

Neuroimaging Findings in Pediatric Dialysis

In addition to neurocognitive function, the impact of CKD has been demonstrated in various neuroimaging and electroencephalographic (EEG) procedures, as noted above. From the approximately 15 or so neuroimaging studies that have been conducted to date, structural analyses via magnetic resonance imaging (MRI) and computerized tomography (CT) have documented the presence of a variety of anomalies including chronic infarct lesions, ischemic watershed zone white matter lesions, early signs of cerebral vascular disease as demarcated by deep white matter hyperintensities and white matter lesions, and cerebral atrophy [90]; however, virtually none of the childhood studies have isolated children on dialysis, or various forms of dialysis, in their descriptions, with the work by Valanne et al. [42] being the one exception thus far.

Electrical conduction dysfunction has also been reported, with EEG abnormalities being reported in 42% of a pediatric cohort with CKD from infancy, and it has been associated with poorer kidney function and severity of anemia in adults [21, 42, 91]. Hurkx et al. [92] found no differences in auditory pathway nerve conduction between children with CKD and children undergoing PD. For the entire combined sample, high inter-peak latencies were found in the somatosensory cortex and were attributed to decreased cortical conduction via the thalamus. Brainstem conduction was normal for the combined group, with no differences noted between those with CKD and those receiving PD; however, delayed conduction was noted in the thalamocortical region for children less than 30 months of age for the combined sample, perhaps being secondary to delayed myelination in very young children with CKD. In addition to specific conduction abnormalities, children with CKD may be at risk for generalized conduction abnormalities which manifest as a seizure disorder as reported in 0% to 20% of children with CKD [92, 93]. The application of these findings to children receiving dialysis, though, remains unknown at present.

Management of Cognitive Dysfunction in Children on Dialysis

Given the chronic nature of ESKD and its associated neurodevelopmental challenges, it is likely that children and adolescents with ESKD are in need of a variety of management strate-

gies. This is true regardless of their treatment modality. There are various medical complications that many of these children experience that interfere with day-to-day functioning (e.g., school absences, medication compliance issues, etc.), and they likely will experience frequent challenges in the school and preschool settings secondary to their cognitive dysfunction and kidney-related medical complications. For example, there are high rates of low birth weight and prematurity in the CKD population, with rates as high as 18%, and these factors can influence brain development and associated cognitive functioning along with the kidney disease. Similarly, there are concomitant high rates of seizure disorders in children with kidney disease, with these rates ranging from approximately 7% to 18% for children on dialysis [85, 94], particularly those receiving HD [95]. These rates increase during dialysis to 29% for children who have had a prior history of seizures. Further, with respect to the presence of seizures pre-dialysis or the manifestations of seizures during dialysis, it is important for the pediatric nephrologist to understand potential adjustments to the anticonvulsant medications that might be required, particularly during the dialysis process, so as to lessen the chance of seizure occurrence [96]. Taken together with these (and other) medical management strategies, the management of the cognitive dysfunction in pediatric ESKD also requires significant attention by the pediatric nephrologist and the interdisciplinary health-care team.

Although there are no evidence-based educational management strategies or interventions explicitly linked to CKD, there are a number of empirically based interventions that have a demonstrated track record in working with children with learning and developmental difficulties. In addition to the necessary medical interventions detailed across many of the chapters in this text, management of the neurodevelopmental challenges also should be considered and implemented via a developmental framework; that is, these should be considered with the developmental level of the child in mind for their most efficacious applicability to a pediatric dialysis

population, and they should be discussed routinely with the family by the interdisciplinary team of professionals caring for the child [97].

Early Intervention

The infant, toddler, and preschool periods of development are critical to the growth of the child. This time period, encompassing birth to approximately 5 years of age, is a remarkable time of development. It is the time when gross motor skills evolve into crawling, walking, running, jumping, and skipping. It is also the time when fine-motor skills evolve into grasping a snack with the rake of a hand to scribbling with a crayon to eventual adaptive skills and other important functions such as dressing and writing. This time period is critical in terms of the ongoing development of cognitive abilities, preacademic skills, and increasingly complex social interactions [98]. As such, these first 5 years of life are at least as important as any other 5-year span in an individual's life and perhaps can influence outcomes across the life span [13, 99].

The quality of neurodevelopmental outcomes also may be dependent on the type and quality of the early intervention services that they receive. The accumulating evidence suggests that the results of early efforts to remediate or attenuate a child's deficits can be successful. Although more evidence exists to support the benefits of early intervention for children at environmental risk [98], research that supports services for young children with biological impairments, such as those receiving dialysis, is also growing. For example, Black et al. [100] examined the influence of home visiting on infants with failure to thrive syndrome using a standardized home intervention curriculum that focused on maternal sensitivity, parent-infant relationships, and child development. This group was compared with a group of typical infants and with a group of other infants with failure to thrive who did not receive home intervention, but were seen in a medical clinic for routine care. At 8-year follow-up, children in the typical growth group were taller and heavier and had better arithmetic scores than the

clinic-only group. The home intervention group had intermediate results. There were no group differences in IQ, reading, or mother-reported behavior problems; however, children in the home intervention group had fewer teacher-reported problems and better work habits than the clinic-only group. How such a program would impact the developmental trajectory of young children with ESKD receiving dialysis remains to be determined; however, such an intervention may be quite applicable to the young dialysis population.

Additionally, it is important to note that there are a number of early intervention programs designed to improve specific developmental areas, such as motor functions, language abilities, and social-emotional skills in the early years [98]. It is suspected that young children with ESKD will respond positively to these types of early intervention approaches and programs. In the meantime, it will be important for pediatric nephrologists to be aware of such programs in their communities, or at least the early intervention programs and professionals, so as to work with their families and local developmental experts in providing the early intervention services that might be necessary for the preschool child with ESKD and receiving dialysis.

School Age

Despite many medical advances in pediatric nephrology, children with CKD are at risk for school-based challenges and failures. Further investigation is needed to potentially improve academic outcomes for this population through hospital-based intervention and special education planning. Although high rates of neurocognitive impairment have been reported, observational studies of school placements have revealed that most children with CKD attend regular education settings with or without special education and that their overall achievement skills are not overly impaired [101]. However, children with ESKD do show increased rates of school difficulties across all subject areas, and they experience increase rates of school absenteeism and grade retentions as shown in Table 34.1. Additional

research is needed to better understand the special education and general learning needs of children with ESKD. There are, however, a variety of evidence-based instructional strategies that are likely applicable to children with ESKD.

Specifically, the interventions that have been developed for various aspects of reading have a clear scientific foundation with numerous studies demonstrating their effectiveness for children with reading disorders. For example, there is a preponderance of evidence to indicate the importance of explicit instruction in the alphabetic principle and phonological processing as critical components to reading intervention for children with reading recognition problems. Indeed, the National Reading Panel [102] showed the effects to be large in magnitude. Similarly, repeated reading interventions have been shown to improve reading fluency [103], and the development and use of strategies have been employed to improve reading comprehension [104]. Similar efforts have shown positive outcomes in the areas of mathematics [105] and written language [106, 107]. Another area that has evolved for children with various neurological and neurodevelopmental disorders is cognitive rehabilitation therapy; however, such computer-based treatments have not been applied to children with CKD or ESKD. The presence of neurocognitive difficulties in this population of children raises the potential for the use of these computer-based treatment strategies, particularly with respect to their applicability to the home, school, and clinic settings [108].

Adolescence and Adult Transition

In addition to many of the treatments available for school-age children, adolescents with ESKD face many barriers during their transition to early adulthood. The transition to adulthood is an important period in human development that requires an individual to increase his/her level of autonomy, find gainful employment, and build social relationships. Childhood-onset CKD/ESKD and the associated medical complications can prevent many adolescents from making this transition and facing these developmental challenges successfully [109]. Improvement of the

current survival rates for adolescents with ESKD of 80% at 10 years must be coupled with successful transition expectations [110, 111].

To date, intervention research geared toward the medical and psychosocial barriers that impede transition to adulthood is in development, and intervention research geared toward understanding the cognitive barriers to transition remains nonexistent. Over 8 years ago, Bell et al. [112] noted the importance of the possible interaction between cognitive functioning and successful health-care transition for adolescents and emerging adults with end-stage kidney disease. They asserted the importance of the cognitive/developmental level of the patient as a key factor in successful transition, along with a host of other factors including available health resources, family functioning, and the need for family education about the challenges of health-care transition. Further, Bell et al. discussed the importance of collaboration and clear communication between the pediatric and adult health-care teams in the transition process, and this will be especially important for the adult nephrologist assuming the care of an emerging young adult receiving dialysis.

In spite of minimal response-to-intervention research within this population, several possibilities exist that might prove instrumental in smoothing the transition for adolescents with ESKD. In addition to the special education issues noted above, Icard et al. [113] examined specific transition issues including vocational rehabilitation services and mental health needs and stressed the need for the development of evidence-based transition programs that would facilitate the movement from late adolescence into adulthood [110]. The issue of medical transition also is critical to this population, particularly given the importance of medication adherence [114] and the treatment of the associated medical needs that will continue into adulthood.

Conclusions and Directions

This chapter outlined the neurodevelopmental challenges of children with ESKD, with a particular focus on the effects of dialysis on the brain.

While it appears that nearly every neurocognitive function can be affected by ESKD and dialysis, the literature is compromised by a variety of methodological issues including small sample sizes, samples of convenience, highly heterogeneous samples (e.g., wide age ranges, different ages of treatment), heterogeneous treatments, and lack of consistency of measurement across studies [77]. Future studies clearly need to address these methodological issues in order to provide a clearer picture of the neurocognitive outcomes in children receiving dialysis.

Despite these methodological problems, it does appear that children receiving dialysis demonstrated significantly lower IQ when compared to controls, and they show a variety of other neurocognitive and learning difficulties as well. Children receiving hemodialysis may be at particular risk for showing neurocognitive impairments and higher rates of seizures, although this will require additional study, especially the possibility that there could be improvement posttransplant. Findings from the available literature also suggest that shorter durations of dialysis and early kidney transplant hold potential for lessening the degree of neurocognitive impairments. The application of developmentally appropriate interventions to optimize their cognitive trajectory and opportunities for independence as adults also is important, particularly as children move closer to ESKD and the possibility of renal replacement therapies. At a minimum, utilization of a multidisciplinary or interdisciplinary team model would be important to assist in managing the shifting developmental needs of the individual with ESKD and his/her family from a life course perspective, with ongoing neurodevelopmental surveillance being a critical component of that approach. Using a multidisciplinary and scientifically rigorous approach, we anticipate the coming decade to provide opportunities to progress from quantifying the developmental challenges to identifying the underlying mechanisms and associated evidence-based interventions for the cognitive dysfunction demonstrated in children requiring dialysis and other renal replacement therapies.

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