Current Advances in Chronic Kidney Disease in Children: Growth, Cardiovascular, and Neurocognitive Risk Factors

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Summary: Linear growth and neurocognitive development are two of the most important differences between adults and children, in terms of clinical issues that must be addressed in patients with chronic kidney disease (CKD). Correction of metabolic acidosis, nutritional deficiency, and renal osteodystrophy improve linear growth, but many children require administration of growth hormone to achieve normal growth. A variety of neurocognitive deficits occur in children with CKD, although there has been an improvement in outcome via improved dialysis, correction of malnutrition, and decreased aluminum exposure. Although growth and neurocognitive development are delayed, cardiovascular complications are accelerated in children with CKD, and are reflected in a dramatic increase in cardiovascular mortality compared with healthy children. Other early cardiovascular complications in children with CKD include left ventricular hypertrophy, cardiac dysfunction, and vascular calcifications.

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Chronic kidney disease (CKD) has a negative effect on linear growth; short stature occurs in the majority of adults who develop CKD during childhood.[1] Growth retardation is especially severe during the first year of life, and thus younger age of onset of CKD is associated with a more severe height deficit.[2] Children who have congenital CKD typically fall below the third percentile during the first 15 months of life and then grow at a rate that allows them to parallel the growth curve, albeit below the third percentile.[3] Growth retardation tends to be proportional to the decrement of GFR,[3] although even children with stage 3 CKD (GFR 30-59 mL/min/1.73 m^2) can have a height below the third percentile.[2] The pubertal growth spurt is delayed, shortened, and associated with a reduced growth velocity, contributing to the loss in adult height.[4] Children receiving dialysis have more profound growth retardation than those receiving conservative management or with a renal transplant.[5] Although growth velocity improves after transplantation, most children do not have catch-up growth, so their height standard deviation score does not improve.[1] Both decreased GFR and steroid use[1] may impair growth after transplantation.

Along with affecting adult height, poor growth in children with CKD is associated with increased morbidity and mortality.[6-8] In a study of children receiving dialysis, each one standard

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Table 1. Causes of Poor Growth in Children With CKD

Intrauterine growth retardation
Metabolic acidosis
Malnutrition
Renal osteodystrophy
Glucocorticoid use
Salt wasting
Perturbations in the GH–IGF-I axis

deviation score decrease in height was associated with a 14% increase in the risk of mortality.[6] Similarly, in patients receiving dialysis or with kidney transplants, the children with moderate or severe growth failure had an increased risk of hospitalization and death.[7] Finally, a height below the first percentile at dialysis initiation was associated with an increased risk of hospitalization and death.[8]

A variety of factors cause growth retardation in children with CKD (Table 1); some are amenable to treatment. Isolated metabolic acidosis, as occurs in children with renal tubular acidosis, causes growth retardation and can be treated with base therapy. Sodium wasting also occurs as a result of renal tubular disorders in children, may contribute to poor growth, and can be treated with enteral sodium supplementation.[9] Similarly, renal osteodystrophy, a potential cause of poor growth and bone deformities in children with CKD,[10] can be treated with dietary phosphate restriction, phosphate binders, and activated vitamin D sterols.[11] The use of activated vitamin D sterols improves growth in children with CKD,[12] but excessive suppression of parathyroid hormone may diminish growth.[13] Inadequate caloric intake in children with CKD, which may lead to malnutrition,[14] is treated with nutritional intervention; tube feeding often is necessary in infants. The positive effect of aggressive caloric intervention on growth has been shown in infants, but not in older children.[9]

GROWTH HORMONE THERAPY IN CKD

Growth hormone (GH), which is secreted by the pituitary gland, is necessary for linear growth during childhood; it mediates most of its actions by stimulating the synthesis of insulin-like growth factor I (IGF-I).[15] Children with CKD have normal or increased levels of GH, but GH is less effective at stimulating linear growth in the setting of impaired kidney function. There are multiple mechanisms that explain the decreased efficacy of GH in children with CKD, including decreased hepatic synthesis of IGF-I,[15] decreased bioavailability of IGF-I owing to higher levels of IGF-I binding proteins,[16] and end-organ resistance to GH.[17]

The resistance to GH in children with CKD can be overcome via administration of recombinant human GH (rhGH). Randomized studies of rhGH in children with predialysis CKD were performed after initial promising results in nonrandomized studies.[18,19] In a 2-year, placebo-controlled study involving 125 prepubertal children, the group that received rhGH had significantly better growth than the placebo group during both years of the study, but the difference was greater during the first year of treatment.[18] Children receiving dialysis respond to rhGH, but the effect is less dramatic than in the predialysis population.[20,21]

There are also a number of studies showing the efficacy of rhGH in children who have short stature after kidney transplantation.[22,23] Along with short-term benefits, rhGH in children with CKD results in improved adult height.[21]

Before use of rhGH, children should undergo correction of metabolic acidosis, renal osteodystrophy, and nutritional deficiencies. Treatment with rhGH should be initiated in children who are below the third percentile for height or who have linear growth below the third percentile. Secondary hyperparathyroidism may worsen with rhGH[20]; parathyroid hormone levels should be monitored before and after initiating therapy.[24]

Intracranial hypertension, which may present with headache, papilledema, visual changes, nausea, or emesis, is a rare complication of rhGH therapy in children with CKD.[25] There is a question about whether rhGH might increase the risk of acute rejection in transplant recipients, but most studies have not supported this concern.[22,23] Despite isolated case reports, there is

no evidence that rhGH increases the risk of malignancy or pancreatitis.[25]

Despite the efficacy of rhGH in correcting short stature in children with CKD, the majority of children who are eligible do not receive this therapy.[26] The requirement for daily injections is an obvious barrier to therapy, and it is clear that psychosocial factors are an important cause of low rhGH utilization.[27] Nevertheless, it appears that rhGH is not offered to some children without obvious contraindications; short girls are significantly less likely to receive rhGH than short boys.[27] Insurance approval may be an important cause of delays in patients receiving rhGH.[27]

CARDIOVASCULAR DISEASE

Cardiovascular mortality in children and young adults with end-stage renal disease (ESRD) is several orders of magnitude greater than nationally reported health statistics for similar age groups. According to the US Renal Data System Annual Report, cardiovascular mortality among pediatric patients with ESRD has been increasing, from 17.7 deaths per 1,000 patient-years at risk in 1991 to 23.4 in 2005.[28] Deaths attributed to cardiovascular disease (CVD) are highest among African American children and young adults on dialysis. In the registry of the North American Renal Trials and Collaborative Studies, 22.8% of 471 deaths in pediatric dialysis patients were attributed to cardiopulmonary causes.[29] Although there is some concern that deaths attributed to CVD in claims data or registries may be misclassified, closer inspection of CVD end points in the US Renal Data System database by Chavers et al[30] confirmed the high prevalence of CVD in this population, revealing that 31.1% of incident pediatric dialysis patients aged 0 to 19 years experienced a cardiac-related event in up to 7 years of follow-up evaluation. Arrhythmias occurred at approximately 91 to 128.6 events per 1,000 patient-years at risk, whereas cardiomyopathy was reported at rates of 42 to 85 events per 1,000 patient-years at risk. Valvular disease and cardiac arrest also were reported, but were less common than arrhythmias and cardiomyopathy.[30] Sudden death in the pediatric CKD and ESRD population may be the result of fatal arrhythmias, possibly related to dilated hypertrophic cardiomyopathies or acute changes in electrolyte balance.

CVD RISK FACTORS IN CHILDREN

In adults, traditional and CKD-related risk factors have been associated with CVD. In adults, traditional risk factors for CVD events include increasing age, white race, male sex, hypertension, left ventricular hypertrophy (LVH), dyslipidemia, diabetes mellitus, tobacco use, physical inactivity, psychosocial stress, positive family history of CVD, and obesity.[31] In children, adolescents are at higher risk of CV events than younger children, and African American race and female sex have been reported to be risk factors for CVD in children and adolescents on dialysis.[30]

HYPERTENSION

Hypertension (HTN), as measured by casual blood pressure or ambulatory blood pressure monitoring (ABPM), accelerates CKD progression and is exacerbated by the decline in kidney function.[32,33] In a North American registry of children with chronic renal insufficiency, children who were hypertensive at the time of enrollment developed ESRD or loss of glomerular filtration rate (GFR) greater than 10 mL/min/1.73 m^2 significantly more often than normotensive children with CKD.[34] In a cross-sectional study of North American children with mild to moderate CKD, HTN was quite common.[35] For systolic blood pressure (BP), 17% had uncontrolled HTN (BP, >95th percentile) and 7% had pre-HTN (BP, 90th-95th percentile). The overall prevalence of systolic HTN (controlled and uncontrolled) was 53%. For diastolic BP, 16% had uncontrolled HTN, and 11% had pre-HTN. The overall prevalence of diastolic HTN (controlled and uncontrolled) was 54%. After adjusting for multiple variables, male sex (predicted risk [PR], 1.7; 95% CI, 1.0–2.6; $P = .03$); nephrotic-range proteinuria (PR, 1.6; 95% CI, 1.1–2.6; $P = .02$), and not using angiotensin-converting enzyme/angiotensin-receptor blocker (PR, 1.5; 95% CI, 1.0–2.3; $P = .06$) were associated with the presence of uncontrolled HTN. The finding that a significant proportion of children with CKD have increased

BP, although about one third of these children were not receiving antihypertensive medication, indicates that HTN, an important risk factor for CVD in pediatric CKD, frequently is undertreated. More aggressively treating hypertension is a clear opportunity to improve and perhaps ameliorate the burden of CVD in children, adolescents, and young adults with CKD. Of note, proteinuria, a putative risk factor for CKD-related CVD in adults, was a significant risk factor for HTN in this baseline pediatric study.[35]

ABPM recently was shown to facilitate a more accurate diagnosis of HTN in children and also to predict hypertensive target-organ damage.[36,37] In small studies in children, abnormalities of ABPM have been associated with target organ damage, including increased carotid intima medial thickness (cIMT) and LVH.[38,39]

LVH

LVH has been reported as a risk factor for CVD in adults. Mitsnefes et al[40] assessed left ventricular mass (LVM) in 25 children with mild-to-moderate CKD, and found that 22% of CKD patients had LVH or developed LVH in 2 years of follow-up evaluation. Eccentric LVH was the most common geometric pattern. Regression analysis showed that a lower initial LVM index and hemoglobin level and an interval increase in intact parathyroid hormone level and nighttime systolic BP (SBP) load independently predicted the interval increase in LVM index.

Mitsnefes et al[41,42] assessed LV function in children with CKD versus controls and found that children with CKD on chronic dialysis and after transplant had impaired diastolic function. An increased LVM index was the only measured independent predictor for diastolic dysfunction in these patients.

DYSLIPIDEMIA

CKD and ESRD are associated with increased circulating concentrations of triglycerides and triglyceride-rich lipoproteins, and decreased concentrations of high-density lipoproteins.[43,44] This pattern of dyslipidemia is atherogenic and therefore is likely to contribute to increased CVD risk. Dyslipidemia increasingly is believed to facilitate the genesis and progression of CKD.[45]

ANEMIA

In adults with CKD, observational evidence shows an association between anemia and LVH.[46] Higher hemoglobin levels have been associated with improved oxygen utilization, exercise capacity, and cardiac function. Evidence supporting cardiac benefits associated with the treatment of anemia in children with CKD is limited, although some reports describe an improvement in cardiac geometry.[47,48] A single, blinded, cross-over trial of 11 children aged 2 to 12 years on dialysis showed an improvement in cardiac index by 6 months and a significant reduction in LVM by 12 months in anemic children treated with an erythropoietin-stimulating agent.[49] Two additional observational studies of patients with severe LVH showed that children with lower Hb levels had more severe LVH, and lower left ventricular compliance.[41]

ABNORMAL CALCIUM AND PHOSPHORUS

CKD is associated with a marked prevalence of arterial calcification in both adults and children.[50] Increased serum levels of calcium and phosphate have been recognized as risk factors for vascular calcification in both observational and interventional studies in CKD. In a number of studies, detection of arterial calcium with electron beam computed tomography or carotid ultrasound has been associated with CVD. In a study of 44 pediatric patients with CKD stages 2 to 4 and 16 patients on dialysis, Mitsnefes et al[51] found that an increased calcium-phosphorus product predicted increased cIMT. Increased serum phosphorus and parathyroid hormone predicted increased arterial stiffness. Thus, vascular abnormalities appear to be present already in children and adolescents during early stages of CKD, and these appear to be related to abnormal calcium-phosphorus metabolism.

CHRONIC INFLAMMATION

Chronic inflammation is a feature of patients with ESRD, and increased levels of inflamma-

tory markers have been detected in both adults and children at earlier stages of CKD.[52,53] Circulating inflammatory cytokines have been suggested as mediators in the progression of CKD and as an important link between CKD and CVD risk factors. Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α, have been linked to increased atherogenesis as well as increased morbidity and mortality among adults with ESRD.[54] Increased circulating levels of IL-6 have been linked to hypertension, LVH, atherosclerosis, and cardiac mortality among adults with ESRD.[55] The balance between the proinflammatory cytokine IL-1 and the anti-inflammatory cytokine IL-1RA also has been shown to predict CV outcome in adult patients. IL-10 is an anti-inflammatory cytokine that is known to attenuate the inflammatory response, and low levels have been found to be associated with increased CV mortality among adults.[56]

A significant number of young adults with childhood onset of CKD have shown systemic vascular atherosclerosis, endothelial dysfunction, and coronary artery disease.[57,58] Local overexpression of the renin-angiotensin-aldosterone system, adrenergic system, and inflammatory cytokines may contribute to cardiac and vascular changes in CKD.

NOVEL CVD RISK FACTORS

In addition to traditional CVD risk factors in CKD, a number of novel risk factors for CVD recently have gained attention. An abnormal birth history is extremely common in children with CKD, particularly those with underlying urologic disease. A growing body of evidence supports the Barker[59] hypothesis, which contends that low birth weight (LBW; <2,500 g) places patients at increased risk for development of a variety of problems including obesity, type II diabetes, and CVD. Likewise, the Brenner hypothesis argues that LBW is associated with a reduction in nephron number, which increases the risk for hypertension and CKD.[60]

LBW or prematurity has been associated with CVD risk factors in children without kidney disease. A study by Bayrakci et al,[61] in which ABPM was performed in 41 children born preterm, showed the preterm group had higher nocturnal systolic BP, increased nocturnal systolic and diastolic BP loads, and blunted nocturnal dipping. In normal children, in a study by Hemachandra et al,[62] infants who were small for gestational age were not at increased risk for high blood pressure at 7 years of age. However, children who crossed weight percentiles upward during early childhood had an increased risk. In a separate analysis of the 29,710 mother-child pairs from the Collaborative Perinatal Project, there was a significant interaction between race and birth weight in predicting SBP ($P = .002$). LBW did not predict increased SBP in blacks.[62]

Recent studies have suggested that low vitamin D levels are highly prevalent in individuals with CKD, and may be an important risk factor for CVD.[63] Vitamin D deficiency is widely recognized in adults with CKD, and recently confirmed in children with ESRD.[64] In one study, 92% of children had 25-hydroxy vitamin D deficiency and 36% had 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) deficiency. Vitamin D is believed to play a role in the development of CVD by decreasing renin levels, controlling inflammation, and down-regulating vascular endothelial cell proliferation.[65,66] In children on dialysis, low vitamin $1,25(OH)_2D_3$ levels have been associated with increased cIMT.[64]

NEUROCOGNITIVE EFFECTS OF CKD

The cognitive development of infants and children with CKD is an area of study that has, until recently, received little attention, with little discrimination between those with ESRD and those with earlier stages of CKD.[67] This is all the more interesting given the long-term and significant clinical manifestations that abnormalities of cognition may have on patient outcome. Early reports, such as those of Rotundo et al[68] and McGraw and Haka-Ikse,[69] revealed findings of profound developmental delay in 60% to 85% of infants with severe renal insufficiency, with delays in gross motor skills and language development being most common.[70] In the former study, 20 of 23 infants showed an encephalopathy characterized by developmental delay, microcephaly, hypotonia, seizures, and dyskinesia.[68] All of this occurred in the setting of a uremic milieu and during a critical period of

brain development that persists through the initial 6 to 12 months of life and that typically is associated with 50% of postnatal brain growth.[71] Subsequent recognition of the crucial role that aluminum exposure and malnutrition played in this scenario and the resultant introduction of improved dialysis water purification techniques, the avoidance of aluminum-containing phosphate binders, and the aggressive use of supplemental feeding methods has led to improved neurodevelopmental outcomes overall. Nevertheless, the finding of nonspecific EEG abnormalities, the possibility of delayed myelination of the somatosensory cortex, and/or the increased risk for central nervous system structural abnormalities (eg, atrophy and infarcts) in some patients remains.[72-74]

In one of several studies that addressed the general development of young patients, Hulstijn-Dirkmaat et al[75] compared the development of 15 toddlers with CKD who were being managed conservatively with that of 16 children who were receiving dialysis therapy. The patients with CKD performed better than those on dialysis as reflected by their achievement of a higher developmental index. Honda et al[76] examined the growth and development of 15 children younger than 2 years of age and receiving peritoneal dialysis (PD) and found that the developmental quotient was normal (>80%) in only 2 patients, although 3 of 4 patients with the lowest developmental quotient suffered cerebral infarctions or Jeune syndrome to account for some of the findings. In one of the larger reports, Warady et al[77] described the neurocognitive status of 28 infants at 1 year of age, all of whom had initiated long-term PD and supplemental tube feedings during the first 3 months of life, with no exposure to aluminum. The general development of 22 (79%) of the infants fell in the normal range and only 1 (4%) patient was categorized as impaired; 12 patients were mildly hypotonic. Finally, Ledermann et al[78] described the outcome of 8 children who initiated PD during infancy, and 2 (25%) of these patients showed developmental delay when evaluated at younger than 5 years of age. Thus, it appears that at least 25% of infants and toddlers who have severe renal insufficiency will show developmental delay, whereas the impact of milder forms of CKD on the neurodevelopment of infants is unknown.

Intelligence Quotient

The availability of intelligence quotient (IQ) data as a measure of cognitive function in older children with CKD has provided additional valuable information.[72,76-80] Honda et al[76] found that at 5 to 6 years of age, the mean IQ of their 9 patients was 80.6 and 6 of the patients scored higher than 85 (within 1 SD of normal mean value) and attended a normal school. Warady et al[77] found that of 19 children retested at older than 4 years of age (mean age, 6.6 ± 1.3 y), 15 (79%) had a normal IQ, although only 72% and 56% of these patients scored in the average range on tests of verbal and nonverbal functioning, respectively. Almost all of these patients had undergone renal transplantation and of the 16 school-aged patients, 15 (94%) were attending school as full-time students in an age-appropriate classroom. Of 8 patients 5 years of age and older in the cohort followed up by Ledermann et al,[78] 2 (25%) showed general developmental delay and were receiving teaching support in a normal school setting. Brouhard et al[81] described a significantly lower IQ in children with CKD when compared with their sibling controls. Most recently, Madden et al[79] reported on the cognitive and psychosocial outcome of 16 infants who began PD during the first year of life, the majority (75%) of whom had a functioning transplant at the time of their reassessment at a mean age of 5.8 years. Ten (67%) children had an IQ that was in the normal range, whereas 13 of 15 (87%) had an IQ score within 2 standard deviations of the norm. Finally, in studies that compared the results of transplanted patients with those remaining on dialysis, Lawry et al[82] found that the mean IQ of the transplanted population was higher than that of the dialysis group (although the results of both groups were in the average range), whereas Brouhard et al[81] conducted a cross-sectional study and did not find any difference in the mean IQ of the 2 patient groups. Improvement in some neurocognitive functions, however, have been seen after transplantation (see later).[80] Thus, this information suggests that children with CKD tend to score lower

than normal children on tests of general cognitive functioning, although the results in many patients can be quite good. Although recent work has provided preliminary support of the concept that an increased severity of CKD correlates with a lower IQ and may help explain some of the differences in outcome noted earlier, additional studies in this area are needed, with particular reference to patients who have only mild-moderate CKD.[81-84]

SPECIFIC NEUROCOGNITIVE FUNCTIONS

In addition to studies focused on the general cognitive development of children with CKD, a number of publications have reported on the evaluation of specific neurocognitive functions. Fennell et al[85,86] conducted many of the early investigations and found that children with CKD had deficits in verbal abstraction abilities and that verbal performance progressively worsened with a greater duration of kidney failure. These investigators also documented that children with CKD showed deficits in visual-motor abilities.[85] In the area of attention and executive function (control processes that are linked to the integrity of the prefrontal cortical regions in the brain and that involve abilities such as problem solving), Fennell et al[85,86] reported that patients with CKD showed poorer sustained attention skills compared with matched controls. Mendley and Zelko[80] reported improvements in sustained attention and mental processing speed 1 year after transplantation. Similarly, Qvist et al[72] found no group deficits in attention when comparing transplant recipients with a normal population, although 24% of patients showed reduced attention spans. Gipson et al[87] recently evaluated 20 children and adolescents and controls and found that the CKD group was deficient in their initiation and sustaining behaviors within the executive function domain, even when controlling for IQ and chronologic age.

Evaluation of memory is of importance because of its critical contribution to success in school and employment. In addition to a prior report by Fennell et al[86] of lower memory scores for tasks requiring immediate recall in CKD patients versus controls, Gipson et al[87] found that children with CKD had significantly lower memory abilities than controls with an emphasis on short-term verbal memory, short-term visual memory, and new learning.

In summary, children with CKD are at risk for impairments of overall cognitive functioning, the development of which may be related to the severity and duration of renal insufficiency, patient age, and associated medical disorders such as hypertension.[88] When cognition is impaired, academic functioning may prove suboptimal with particular reference to skills in reading, writing, and mathematics. These findings emphasize the necessity of early screening for deficits with a standardized battery of neurocognitive assessments and aggressive intervention when deficits are detected.[83,89,90] Persistence of the neurocognitive impairment into adulthood is possible and can be especially problematic.[91] Ideally, multicenter initiatives, such as the Chronic Kidney Disease in Children study,[92] will soon provide additional valuable insights into the development and evolution of neurocognition across the spectrum of renal insufficiency in this vulnerable population.

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