Nephrologic Issues in Children with Developmental Disabilities

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This article, reviewing renal involvement in children with developmental disabilities (DD), is divided into two distinct parts. The first section considers children without primary renal disease who have DD and looks at renal involvement in this population. The second part reviews the DD that is unique in children who have primary renal involvement.

RENAL INVOLVEMENT IN CHILDREN WHO HAVE DEVELOPMENTAL DISABILITIES WITHOUT PRIMARY RENAL DISEASE

Structural Renal Involvement

Structural renal involvement is common in children who have genetic syndromes. As a rule, in children who have genetic syndromes, renal structural involvement includes various renal malformations. These may include, separately or in combination, renal dysplasia or hypoplasia. This is caused by inadequate nephrogenesis in the first trimester of pregnancy that may present clinically as polyuria with polydipsia caused by a renal concentrating defect. This can be associated with progressive loss of renal function with physiologic complications of metabolic acidosis, anemia, secondary hyperparathyroidism, and growth impairment. Renal imaging may reveal small-for-age renal size with poor corticomedullary differentiation or increased echogenicity. This diagnosis is based, not upon histology, but on clinical suspicion of the disease.

Other renal involvement may include abnormalities of the renal location, including cross-fused ectopia or horseshoe kidneys. Whereas these are interesting findings, unless they are associated with vesical ureteral reflux (VUR) or renal dysplasia, they are not clinically concerning. Single renal formation (ie, absence of a single kidney), multicystic dysplastic kidneys (unilateral malformed kidney with little to no renal perfusion),

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and unilateral or bilateral VUR should be considered in children who have genetic causes of DD. In newborns with a single kidney or misplaced kidneys most nephrologists recommend a voiding cystourethrogram (VCUG) to evaluate for VUR. If present, in most cases, VUR can be treated with prophylactic antibiotics until the VUR naturally resolves. Indication for ureter reimplantation surgery includes breakthrough urinary tract infections (UTI) or worsening renal function or VUR over time.3

**Physiologic Renal Involvement**

The primary complications seen in children who have DD without primary renal disease include recurrent UTI, hypertension, and increased risk for kidney stones.

**Urinary tract infections**

Recurrent UTIs in children who have DD need to be evaluated. It is important to ensure that the child truly has a UTI. Recurrent dysuria can be seen in children who have UTIs but also in children who have renal stones (or those at increased risk for renal stones) or constipation. The gold standard of UTIs holds true in this population as in others; that is, a catheterized urine sample should be sent for culture and sensitivity to confirm the UTI diagnosis.

Once a diagnosis of UTI is made, the evaluation should focus on structural renal diseases as noted previously. This includes renal imaging (ultrasound will suffice in most cases) and a voiding cystourethrogram (VCUG). Many programs recommend that VCUGs be ordered only under the coverage of treatment or prophylactic doses of antibiotics to prevent back flushing of infected urine during the VCUG if VUR exists. If structural renal disease exists in the face of recurrent UTIs, then prophylactic antibiotics are recommended until resolution of the VUR or other identified risk factors. Additionally, constipation needs to be considered as an independent risk factor for UTIs. Stool hoarding or other causes of constipation can exacerbate voiding dysfunction, setting the child up for recurrent UTIs.

**Hypertension**

Hypertension can be seen in children who have DD. Similar to UTIs, it is paramount that hypertension is confirmed appropriately. The standard for blood pressure (BP) evaluation is a BP check in the arm and not the leg. Further, the BP cuff needs to cover two thirds of the area of the arm. A BP cuff that is too small artificially elevates a BP reading, but a BP cuff too large will not lower a BP reading artificially. Automatic BP machines may sense muscle fasciculation that may be registered as BP readings by the machine. In children who have muscle spasticity, a manual BP reading may be needed to avoid false blood pressure readings.

Etiology of hypertension in this population may be related to medicine (eg, stimulants used for attention deficit–hyperactivity disorder [ADHD]), primary renal disorder, electrolyte disorder, hormonal dysfunction, or a central nervous system [CNS] disorder).4 A complete evaluation includes a urinalysis (looking for blood or protein), blood work (includes electrolytes, creatinine, calcium with an albumin or an ionized calcium, and thyroid function), and renal imaging. Also, if the child has a risk for CNS disorder-induced hypertension (eg, ventriculoperitoneal [VP] shunt) or has associated bradycardia, then an evaluation for high intracerebral pressure needs to be accomplished. In children on stimulants, the only true way to evaluate if the stimulants are the cause of the elevated BP is to discontinue the medication and allow the effect to wash out for 5 to 7 days (two to three half lives of the medication) to see if the situation resolves.5

Treatment of identified hypertension includes removing the offending cause if possible. If structural renal or primary renal effect is the etiology, then an evaluation by
a pediatric nephrologist is in order. In this setting, all classes of antihypertensive agents may be reasonable as therapeutic options.

If the hypertension is caused by hypercalcemia, then the etiology of hypercalcemia determines the specific treatment. This evaluation includes a review of sources of vitamin D and A that raise the calcium level and evaluation of the phosphorous and magnesium and the parathyroid hormone (PTH) and thyroid hormone levels. In patients on ketogenic diets, rarely hypercalcemia can be a cause. In patients who have poor mobility, immobilization-related hypercalcemia needs to be considered. In children who have resistant hypercalcemia with normal phosphorous, magnesium, PTH activity, and vitamin D and A levels, management with bisphosphonates should be considered.

If the etiology of the hypertension is spasticity or a nonlife-threatening CNS disorder, use of centrally acting agents (eg, clonidine) may be helpful. Experience suggests that the use of clonidine as a transdermal patch may allow for ease of administration with minimal need for oral medications. Alternative to centrally acting agents in this setting are the beta-blocker agents. In children who have catecholamine surges with secondary tachycardia and hypertension, this class of medications easily blunts this effect.

Renal stone formation or stone risk
The clinical presentation of renal stones or increased risk for renal stones includes dysuria, urinary gravel seen by the guardian, and microscopic or macroscopic hematuria. The evaluation is based upon a high suspicion of this risk in addition to renal imaging and urine collections to evaluate the etiology.

Risk factors for stone risk or formation include family history of the same, ketogenic diet, medications (eg, topiramate), lack of weight bearing, and a lack of access to extra water. Often in severely neurologically affected children, multiple risk factors combine as additive risks for stone formation. The lack of weight bearing allows for an increased loss of bone calcium over time. Therefore, exercise is needed to help prevent these phenomena.

Metabolic acidosis (caused by ketogenic diet or medicines [eg, acetazolamide]) or medications that induce calcium wasting (eg, topiramate) are additive risks in this population. Whereas these therapies are helpful for seizure disorders, they are not without renal risk. To avoid complications of these approaches, one needs to evaluate for metabolic acidosis early in the course of therapy.

Children who undergo a ketogenic diet may become hypophosphatemic, with resulting hypercalcemia and hypercalciuria. Evaluation and normalization of the serum phosphorous are needed for prevention. Children who have an induced ketosis caused by ketogenic diet develop metabolic acidosis. This metabolic acidosis results in calcium loss from bone (that can be exacerbated because of lack of mobilization) with resulting hypercalciuria. Treatment and correction of the metabolic acidosis with sodium citrate or sodium bicarbonate lessen this effect without having a negative impact on the benefit of the ketogenic diet.

Children receiving topiramate may induce a proximal tubular defect with phosphorous wasting and metabolic acidosis. This can be corrected readily, and complications can be prevented by attention to normalization of the serum phosphorous and bicarbonate with appropriate supplementation. Correction of these metabolic consequences does not impact the effectiveness of this medication.

The most important treatment of children at risk for stone disease is access to water. Concentrated formulas and immobility inhibiting individuals to get water on their own will predispose patients to increased risk for the formation of renal stones. Adding extra water to a child’s diet will not impact upon the benefit of the diet (eg, ketogenic diet) but will lessen the risk of stone formation for that child.
RENAL INVOLVEMENT IN CHILDREN WHO HAVE DEVELOPMENTAL DISABILITIES WITH PRIMARY RENAL DISEASE

The true incidence of chronic kidney disease (CKD) in children is unknown. At least 50% of children who require dialysis or transplantation (end-stage renal disease [ESRD]) before adulthood have CKD from birth. Most transplant programs transplant children at 20 kg of body weight or greater. As an infant or small child approaches the need for dialysis, the mortality and morbidity are greater after successful renal transplantation. Therefore, there is an ongoing push to maximize growth in these children to reach to the size of safe transplantation.

Over 90% of these children have renal dysplasia that is associated with polyuria and polydipsia. Data show that infants who have severe CKD (stages 3 or higher) require approximately 30% to 40% more nutrition than their non-CKD counterparts for optimal growth. Further, because of their polyuria, these children require approximately 150 to 200 mL/kg/d of fluid to keep them euvoletic. This, a dilute formula that is low in potassium and phosphorous (breast milk, PM 60/40), allows for a reasonable balance between adequate nutrition and volume. The difficulty is that infants and small children who have CKD have a 30% or greater incidence of gastroesophageal reflux (GER) when compared with their non-CKD counterparts. This need for large volume in children who have GER increases the risk for aspiration pneumonia and failure to thrive (FTT). The treatment in many infants and children who have significant GER is to concentrate their feedings, but this results in a large solute load to these children, making them more polyuric and more at risk for FTT. Therefore, many programs have a gastric feeding tube (g-tube) placed in these infants as a way to deliver sufficient nutrition. Because of the severe GER in these infants, a Nissen fundoplication commonly is performed at the same time to prevent severe GER.

Although the use of a g-tube and Nissen fundoplication allows for sufficient delivery of nutrition, they do increase the risk for eating, speech, and oral motor delay. Early intervention with feeding therapy and speech therapy may be needed to help these infants and small children acquire and maintain these skills as part of normal development.

Factors that contribute to DD in children who have CKD also include frequent hospitalizations because of infections, surgeries, and in general medical and nutritional care. Many children’s hospitals use play therapists to help maintain a normal environment for the child to be nurtured despite the presence of the medical system that surrounds him or her.

The physiologic and metabolic consequences of CKD predispose to DD if not recognized and treated. Metabolic acidosis complicates CKD, and if untreated, results in growth impairment. Anemia associated with CKD, if untreated, may impact upon school performance and growth. Untreated secondary hyperparathyroidism of CKD can result in poor bone maturation, bowed legs, gait disturbances, growth impairment, and pathologic fractures. In the current era of CKD therapy in children, if identified, these metabolic disturbances can be treated readily, avoiding these complications.

Also, school performance appears to be affected in children who have CKD. The etiology of these delays is multifactorial and includes disruption in school attendance caused by dialysis treatments and medical appointments and cognitive impairment with learning disabilities. Pediatric nephrology programs are aware of these infants and children at risk and often use community- and medical-based resources to assess the degree of need and evoke involvement when needed.
SUMMARY

Children with DD who do not have underlying renal disease can have a myriad of renal complications that need to be addressed and treated if present. Children who have underlying CKD, especially infants, are at risk for DD because of the treatment of their underlying disease. Both of these unique groups of children require attention to the relative risk of renal and physiologic involvement, and resources need to be identified for treatment success. As noted with many children who have special needs, a team effort involving pediatric subspecialties trained in these areas helps coordinate appropriate care and improve outcome.

REFERENCES
