



Renal Disease: Clinical Presentation in Children

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Abstract

Renal disease is a major concern in children. Pediatricians should be familiar with the modes of presentation of renal disease in children and should have a high index of suspicion for asymptomatic disease. Early diagnosis and treatment of renal disease in children contributes to the prevention of chronic kidney disease. Patients with renal disease may present with Congenital Anomalies of the Kidney and Urinary Tract (CAKUT); signs and symptoms of renal disease; abnormal urinalysis; urinary tract infection; water, electrolyte and acid-base disturbances; glomerular disease; renal tubular disorders; hypertension; decreased renal function; and renal involvement in systemic diseases. Physicians may initiate evaluation and treatment of kidney disease depending on their comfort level. Patients who need team work or invasive studies, those with severe renal disease or decreased renal function, and those with parental anxiety should be referred to the pediatric nephrologist.

Keywords: Renal disease; Congenital anomalies; Urinary tract infection; Glomerulonephritis; Hypertension

Abbreviations

BP: Blood Pressure; CAKUT: Congenital Anomalies of the Kidney and Urinary Tract; CKD: Chronic Kidney Disease; GN: Glomerulonephritis, HT: Hypertension; NS: Nephrotic Syndrome; sg: Specific Gravity; UTI: Urinary Tract Infection; VCUG: Voiding Cystourethrogram

Introduction

Renal disease is a major cause of concern in children [1-3]. The use of routine prenatal ultrasonography has created a new challenge to the pediatrician due to the increase in the diagnosis of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Pediatricians should have knowledge of the modes of presentation of renal disease in children, and a high index of suspicion in patients with asymptomatic disease. Hematuria, proteinuria, and fluid and electrolyte disturbances are the most common reasons for referral to the pediatric nephrologists [4]. Other reasons include Nephrotic Syndrome (NS), Chronic Glomerulonephritis (GN), Urinary Tract Infection (UTI), Hypertension (HT), acute GN, and CKD. Early diagnosis and treatment of renal disease in children contributes to the timely treatment and prevention of CKD. I will discuss here the clinical presentation of renal disease in children and the role of the pediatrician.

Presentation of Patients with Renal Disease

Patients with renal disease may present with (1) CAKUT, (2) signs and symptoms of renal disease, (3) abnormal urinalysis, (4) UTI, (5) water, electrolyte and acid-base disturbances, (6) glomerular disease, (7) renal tubular disorders, (8) HT, (9) decreased renal function and (10) renal involvement in systemic diseases. Since renal disease may be asymptomatic, a thorough abdominal examination, Blood Pressure (BP) measurement, and a urinalysis should be a part of every routine medical examination of children. Laboratory and imaging studies are utilized also to help with the diagnosis and management of the renal disease.

Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

CAKUT consist of a wide range of structural malformations that result from a defect in the morphogenesis of the kidney and urinary tract. They are the most common cause of all birth defects (25%) and affect 5% to 10% of the population [5]. They are also the most frequent malformations detected by prenatal ultrasound. Prenatal diagnosis of CAKUT by ultrasonography as early as 12 to 16 weeks' gestation gives physicians the chance to initiate therapy for urinary tract obstruction in order to prevent pyelonephritis, renal calculi, HT, and CKD.

The most common phenotypic forms of CAKUT include hydronephrosis, renal agenesis, renal hypo-dysplasia, multicystic dysplastic kidney, ureteropelvic junction obstruction, megaureter,

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duplicate ureter, vesicoureteral reflux and posterior urethral valves. Antenatal hydronephrosis (dilation of the fetal renal collecting system) occurs in 1% to 5% of pregnancies. In most affected patients, it is transient with no clinical significance, but it could be also a sign of underlying severe fetal urinary system anomalies.

CAKUT which are the most common cause of CKD in children, are associated with congenital anomalies of the cardiovascular, gastrointestinal and central nervous systems, as well as other organ systems in about 60% [5-7]. In addition, CAKUT should be suspected in children with UTI, malformation syndromes and chromosomal aberrations (20%). A coordinated effort among professionals in the disciplines of obstetrics, neonatology, pediatric nephrology and urology is crucial in diagnosing and treating these conditions in a timely manner. The severity of the abnormality and prognosis will impact decision making during pregnancy and immediate postnatal period. Genetic studies of these patients and their families are of utmost importance, as nephrogenesis of the kidney and urinary tract is governed by hundreds of developmental genes [5].

Signs and Symptoms of Renal Disease

Renal disease in children may be asymptomatic and detected during a routine physical examination [8]. Unexplained fevers, vague pains, anemia, gastrointestinal symptoms, abdominal mass, edema, HT, and metabolic acidosis may be early signs of kidney disease. The first signs of CKD may be anorexia, lassitude, anemia, growth failure, HT, and abnormal retinal changes. CKD and renal tubular disease should be ruled out in any child presenting with failure to thrive. UTI and obstructive uropathy present with frequency, urgency, dysuria, urinary retention, and suprapubic pain.

Children have different voiding patterns at different ages. Unusual patterns or symptoms might suggest various conditions. Frequency (frequent urination) may suggest a UTI. Polyuria (the passage of a larger than normal amount of urine) indicates a decrease in urine-concentrating ability and may suggest diabetes mellitus, diabetes insipidus, and CKD. A fasting urine specific gravity [SG] or water deprivation test should be performed in any child with polyuria and decreased random urine SG. A random urine [SG] of greater than 1.020 in the absence of proteinuria and glucosuria excludes a urine concentration defect. Decreased urine concentrating ability may be seen in patients with chronic pyelonephritis, hydronephrosis, renal cystic disease, and sickle cell nephropathy. Dysuria or pain on urination is one of the symptoms of UTI or urethritis. Nocturia (awakening at night to pass urine) in older children may be normal, or may be due to a reduced urine concentrating ability. Enuresis (nocturnal incontinence) is defined as bedwetting since birth. Affected patients usually have a family history of this condition and initially require no investigation other than a urinalysis and urine culture. Further evaluation may be required in children with secondary enuresis and those with primary enuresis persisting beyond age 12 years. The sudden onset of daytime urinary frequency occurring in toilet trained schoolchildren, especially boys is referred to as Pollakiuria (Greek pollakis, meaning "often"). Affected children usually have a normal physical examination, urinalysis, and urine culture and require no further investigation. This condition requires no treatment and may last from a few days to few weeks.

Renal diseases are usually painless; however, cystitis and prostatitis may produce gradual suprapubic pain. Renal calculi may present with colicky abdominal or flank pain. Infection or inflammation of the renal parenchyma may cause flank pain. Pain may also be caused by

renal and bladder traumatic injury.

The most common abdominal masses of renal origin include hydronephrosis; multicystic, dysplastic, or polycystic kidney disease; renal vein thrombosis; Wilms tumor; and neuroblastoma.

Abnormal Urinalysis

Patients with kidney disease may present with urine abnormalities. A carefully performed urinalysis offers important information regarding kidney disease [9]. A first voided specimen is more likely to show formed elements and bacteria. Urine culture requires a clean-catch midstream specimen. The American Academy of Pediatrics no more recommends a routine dipstick urinalysis in children however; it clearly states that the decision to perform routine dipstick urinalysis ultimately rests with the primary care physician.

The most common abnormalities seen on urinalysis are hematuria and proteinuria. Hematuria may be gross, or microscopic. Isolated, asymptomatic microscopic hematuria in the absence family history of renal disease or hearing loss is usually a benign finding; however, persistent hematuria should be investigated. Initial investigation consists of urinalysis and audiogram. Since recurrent benign hematuria, Alport syndrome, IgA nephropathy, and other forms of glomerular disease may be familial, a urinalysis and audiogram should be performed also on immediate family members. Other tests may include blood chemistries, quantitative urine protein determination, creatinine clearance and imaging studies. Gross hematuria may be seen in patients with recurrent benign hematuria, IgA nephropathy, Alport syndrome, membrano-proliferative GN, kidney stones, CAKUT and other renal conditions.

After orthostatic proteinuria has been ruled out, persistent asymptomatic proteinuria with or without microscopic hematuria, red blood cell casts, or a family history of renal disease requires additional evaluation. A 24 h urine protein (quantitative) or urine protein/creatinine ratio (semi quantitative) (<0.2 in normal individuals) may be used to measure protein in the urine. Significant proteinuria (>1 g/1.73 m²/d) or proteinuria associated with abnormal RBC morphology, decreased renal function, HT, decreased serum complement level, or manifestations of systemic disease suggest glomerular disease and may be an indication for a renal biopsy. Patients with severe GN, nephrosclerosis, SLE, and amyloidosis usually have severe proteinuria (>4 g/1.73 m²/d). Moderate proteinuria (0.5 to 4 g/1.73 m²/d) may be seen in the above listed conditions as well as in diabetic nephropathy and urinary tract disease. The proteinuria found in chronic GN, renal tubular disorders, and polycystic kidney disease is usually mild (<0.5 g/1.73 m²/d). Nephrotic proteinuria is >50 mg/kg/d.

Pyuria may originate anywhere in the urinary tract. It usually suggests UTI, but it may be seen also with any inflammatory process of the kidney and urinary tract as well as in patients with trauma, renal calculi, CAKUT with or without obstructive uropathy, and Kawasaki disease. Abnormalities in urine color or smell, glucosuria, casts, crystals and others should be investigated. It is important to keep in mind that an abnormal urinalysis may be the only presenting sign in chronic GN.

Urinary Tract Infection (UTI)

UTI, which is one of the commonest bacterial infections in children, may cause long term morbidity. It occurs in 2% of boys, 8% of girls prior to sexual activity, and 7% of febrile infants [10,11]. UTI

often presents with nonspecific symptoms in younger children such as unexplained fevers, gastrointestinal symptoms, and irritability. The possibility of UTI should be considered always in a febrile infant with no apparent cause for the fever. The diagnosis of UTI should be based on the presence of pyuria and a positive urine culture. Suprapubic tap or urethral catheterization should be considered when contamination is suspected in a bagged urine sample. It is important to have an accurate diagnosis in every child with UTI, since febrile upper UTI (acute pyelonephritis), lower UTI (cystitis) and asymptomatic bacteriuria are different entities with different epidemiology, treatment and prognosis. Prompt and adequate treatment of UTI is of paramount importance to prevent renal scarring, although published data fail to detect a strong relationship between childhood UTI and decreased renal function in adults.

While there is disagreement on when to perform imaging studies in patients with UTI, these studies should be considered with recurrent and atypical infections such as a seriously ill child, poor urine flow, abdominal or bladder mass, elevated serum creatinine, septicemia, failure of antibiotic treatment within 48h and an infection with a non *E. coli* organism [10].

Water, Electrolyte and Acid-Base Disorders

The kidney plays a critical role in the maintenance and regulation of acid-base and electrolyte homeostasis which is vital for proper functioning of the human body. Kidney dysfunction compromises these regulatory functions resulting in alterations in electrolyte and acid-base balances [12]. Water, electrolyte and acid-base disturbances are more common in infants and children than adults, and present with a complex clinical picture and variable symptoms including nausea, vomiting, diarrhea, decreased fluid intake, irritability, lethargy, weight loss, dry skin and mucous membranes, rapid pulse, seizures, and coma. Dehydration is the result of water deprivation, while edema results from extracellular fluid expansion. Treating physicians should be familiar with the intricacies of the diagnosis and management of these disorders and should refer severely affected patients immediately to a hospital that can provide expert care.

Glomerular Disease

Glomerulonephritis (GN) is an acquired pediatric renal disorder commonly encountered in clinical practice [13]. Although glomerular disease is less common in children and adolescents than in adults, the disease remains a common cause of CKD in children. Pediatric glomerular disease may present with acute GN, GN associated with systemic diseases, NS, or chronic GN. Acute GN in children usually runs a benign course and presents with hematuria, mild to moderate proteinuria, HT, and edema. Often, it can be treated by primary care physicians on an ambulatory basis; however, patients with oliguria, hyperkalemia, NS, cardiac overload, and renal insufficiency may have to be referred. The presence of arthritis, rash, HT, hematuria, and proteinuria may suggest a GN associated with a systemic disease. IgA nephropathy is probably the most common type of chronic GN in adults and children.

NS which occurs in about 1/50,000 children per year is characterized by proteinuria of 40 mg/m²/h (50 mg/kg/d or a protein/creatinine in a random urine >2) and serum albumin less than 2.5 g/dL. Minimal change NS is the most common form in children, and is characterized by response to corticosteroids and good prognosis. Patients who are steroid-resistant or dependent, those with a suspected structural glomerular abnormality, and those with findings

suggesting a systemic disease should be referred to a pediatric nephrologists as they usually require a kidney biopsy and knowledge of the most effective therapeutic regimens.

Renal Tubular Disorders

Renal tubular disorders are rare and complex disorders. They usually present with failure to thrive, polyuria, glucosuria, aminoaciduria, phosphaturia, acidosis, rickets, nephrocalcinosis, hypokalemia and inability to concentrate urine. These disorders include renal glucosuria, Fanconi syndrome with or without cystinosis, cystinuria and other aminoacidurias, renal tubular acidosis, nephrogenic diabetes insipidus, Bartter syndrome, and others [14,15]. Increasing awareness of primary care physicians about tubular disorders will ensure timely referral, early diagnosis and better outcome.

Hypertension

HT in children and adolescents is defined by BP levels persistently greater than the 95th percentile for that individual, based on height percentile, age, and gender, on at least 3 separate occasions [16]. HT affects 2.6% of children with normal BMI vs. 10.7% among obese children (BMI >95th percentile), emphasizing the important role of obesity and the metabolic syndrome in the pathogenesis of HT [17]. Blood pressure should be measured routinely in every child starting at age 3 years and when indicated. Young children are more likely to have an identifiable cause for HT (renal, cardiac or neuroendocrine abnormalities) however, essential HT accounts for over 85% of HT between the ages of 12 and 18. Headache, difficulty sleeping, and tiredness are the most common symptoms of HT in children. Severe persistent HT should be investigated promptly and thoroughly. Pediatricians may initiate the evaluation on children with persistent mild to moderate HT; however, severe or malignant HT requires comprehensive evaluation and prompt antihypertensive therapy.

Decreased Renal Function

Azotemia is elevated serum urea nitrogen, renal failure is reduction in renal function, and uremia is the syndrome that encompasses the overt consequences of CKD (anemia; osteodystrophy; and various manifestations in the central nervous, gastrointestinal, and other systems). The most commonly used biomarkers to monitor renal function are serum creatinine and blood urea nitrogen.

Acute kidney injury is an abrupt severe reduction in glomerular filtration. It is characterized by oliguria (urine <0.5 mL/kg/h) or anuria and azotemia. A patient presenting with the preceding findings, HT, gross hematuria, electrolyte disturbances, particularly hyperkalemia and acidosis, and volume overload should be referred immediately to the pediatric nephrologist. The etiology of acute kidney injury must be identified as early as possible since clinical evaluation, management, and prognosis vary with the specific etiology. Moreover, many causes of acute kidney injury may be reversible.

CKD (the stage at which the kidneys are irreversibly damaged and unable to maintain the body homeostasis) presents with history of underlying renal disease, growth delay, anemia, renal osteodystrophy, or small contracted kidneys [18]. While CAKUT is the main cause of CKD in young children, GN is the prevalent cause in older children. Low birth weight, prematurity, obesity, diabetes, and adolescent smoking are risk factors for the development of CKD in children. Patients with the diagnosis of CKD stage 5 (glomerular filtration rate <15 mL/min/1.73 m²) invariably progress to end-stage renal disease,

requiring long-term dialysis and renal transplantation. Because many causes of CRF in children are potentially preventable (CAKUT and UTI), early diagnosis and treatment of these conditions are of utmost importance.

Renal Involvement in Systemic Diseases

A variety of systemic diseases in children may affect the kidney. Acute onset renal disease may occur with vasculitis such as Henoch-Schönlein purpura and systemic lupus erythematosus, remote infection elsewhere in the body such as hemolytic uremic syndrome and staphylococcal bacteremia, and chronic diseases such as sickle cell disease, diabetes mellitus and malignancy. Diabetic nephropathy is uncommon in childhood as it requires decades of ongoing injury to the microvasculature. Childhood malignancies such as abdominal lymphomas may be associated with renal disease. Certain chemotherapeutic agents are nephrotoxic, and therapy of childhood malignancies may produce tumor lysis syndrome and acute kidney injury.

Systemic diseases associated with glomerular disease may present with fever, arthritis, anemia, hematuria, proteinuria, HT, NS and reduced renal function. The extent of renal involvement may not be clinically apparent and patients need to be referred to the pediatric nephrologist for diagnostic tests including kidney biopsy, which contributes significantly to the diagnosis of collagen disease and other systemic diseases.

The Role of the Primary Care Physician in the Workup and Management of Children with Renal Disease

In this era of managed care, primary care physicians find themselves performing some tasks that have traditionally been performed by specialists. Physicians may initiate evaluation and treatment of kidney disease according to their comfort level. They should keep a high index of suspicion for UTI and renal disease, and take a detailed patient and family history, perform a thorough physical examination including BP measurement, and exclude the presence of systemic disease. They can also order urinalysis (on patient and if indicated, on family members), urine culture, blood (blood urea nitrogen, creatinine, electrolytes, serum complement, quantitative proteinuria, creatinine clearance, and others as needed), imaging studies as indicated (renal ultrasound, VCUG, renal scan, and others), and screen for orthostatic proteinuria, renal tubular disorders, and others. Depending on their comfort level, physicians may treat and follow patients with UTI, uncomplicated acute GN, and conditions not associated with acute or progressive deterioration of renal function (minimal change NS, mild CAKUT, and others).

Pediatricians may have to refer patients with persistent unexplained hematuria and non-orthostatic proteinuria, HT, decreased renal function, renal tubular disease, NS, atypical or persistent GN, unexplained and severe acid-base and electrolyte abnormalities, glomerular disease that is likely to progress, systemic diseases associated with progressive renal disease, genetic and CAKUT likely to produce progressive renal damage, and CKD to the pediatric nephrologists. Patients needing team work (urologist, geneticist, dietician, social worker) or invasive studies such as kidney biopsy, and those with parental anxiety should be referred to the pediatric nephrologist.

Conclusion

Renal disease is a major cause of morbidity in children.

Pediatricians and primary care physicians should be familiar with the modes of presentation of various renal conditions in children and should have a high index of suspicion in patients with asymptomatic disease. Early diagnosis and treatment of renal disease in children contributes to the prevention of chronic kidney disease. Primary care physicians may initiate evaluation and treatment of kidney disease depending on their comfort level. Patients who need team work or invasive studies, those with severe renal disease or decreased renal function, and those with parental anxiety should be referred to the pediatric nephrologists.

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