An overview of kidney diseases in children

Abstract

The 11th of the WKD 2016 on March 10, is dedicated to children, aiming to increase awareness of diseases in this specific subgroup of population. Renal problems in children may be inborn or acquired, acute or chronic and sometimes are associated with systemic diseases. In many cases the clinical signs and symptoms may be minor or even absent making renal disease suspicion and identification difficult. In all cases early detection and treatment and adequate follow-up are major factors of better outcome. In this review, we discuss the main causes of acute and/or chronic renal diseases in children. We particularly focus on presenting specificities of these conditions in childhood population and practices of prevention and early diagnosis.

Key words: acute kidney disease, children, chronic kidney disease

Introduction

World Kidney Day (WKD), is an annual event which is jointly organized by the International Society of Nephrology and the International Federation of Kidney Foundations. The 11th Campaign of the WKD 2016 on March 10, is dedicated to children, aiming to increase awareness of diseases in this specific subgroup of population. Renal problems in children may be inborn or acquired, acute or chronic and sometimes are associated with systemic diseases. Considering their severity may be treatable disorders without long-term consequences, at least in cases of early diagnosis, or life-threatening conditions. Acute kidney injury may be observed in severely ill children hospitalized in intensive care units or in community population. In many cases the clinical signs and symptoms may be minor or even absent making renal disease suspicion and identification difficult. However, in all cases early detection and treatment and adequate follow up are major factors of better outcome. In this review, we discuss the main causes of acute and/or chronic renal diseases in children. We particularly focus on presenting specificities of these conditions in childhood population and practices of prevention and early or innovative, if available, diagnosis.
Causes of kidney diseases in children

The main causes of kidney diseases in children are summarized in table 1. Under the age of 4 years the congenital anomalies of the kidney and urinary tract (CAKUT) and inherited diseases are the major causes of kidney disease. Between ages 5 and 14, kidney dysfunction is most commonly associated with inherited diseases, nephrotic syndrome, and systemic diseases, whereas between ages 15 and 19, glomerular and systemic diseases are the leading causes and hereditary diseases become less common.

Table 1. Main categories of causes of kidney diseases in children
1. Congenital anomalies of the kidney and urinary tract
2. Inherited diseases
3. Glomerular diseases-nephrotic syndrome
4. Vascular and interstitial diseases
5. Systemic diseases

Congenital anomalies of the kidney and urinary tract (CAKUT)

The true incidence of urinary tract anomalies is difficult to ascertain, as many of them are asymptomatic and therefore undetected. However, the wide use of antenatal ultrasounds during the last decades has shown that abnormal development of renal parenchyma may lead to a wide range of pathologic entities and constitute approximately 20-30% of all anomalies identified in the prenatal period. The overall rate of CAKUT in live and stillborn infants is 0.3 to 1.6 per 1000 and deaths from genitourinary anomalies are estimated 0.5% of all causes of infant mortality. The incidence has been reported higher in offspring with a family history of CAKUT and maternal history of either renal disease or diabetes. Renal malformations are associated with nonrenal congenital anomalies in about 30% of cases and a combination of CAKUT and nonrenal anomalies are found in more than 500 described syndromes. Moreover CAKUT is the major cause universally of chronic kidney disease in children and accounted for 30-50% of cases of end-stage renal disease (ESRD) in children. So, it is important to diagnose these anomalies and initiate therapy to minimize renal damage, prevent or delay the onset of ESRD, and provide supportive care to avoid complications of ESRD. In table 2 are summarized the most common CAKUT in children.

Table 2. Congenital anomalies of the kidney and urinary tract
1. Anomalies of renal parenchyma
   a. Renal dysplasia/hypoplasia
   b. Renal agenesis
   c. Cystic renal diseases
2. Disruption of the normal embryologic migration of the kidneys
   a. Renal ectopia (eg, pelvic kidney)
   b. Fusion anomalies (eg, horseshoe kidney)
3. Anomalies of the collecting system
   a. Complete or partial duplication of collecting system
   b. Junction obstructions
   c. Abnormalities of the ureter (eg megaureter, ectopic ureter, ureterocele, or vesicoureteral reflux)
   d. Bladder extrophy
   e. Posterior urethral valves

Congenital anomalies of the kidney and urinary tract may affect size, structure or position of the kidneys and are bilateral or unilateral. Aberration of quantitative development leads to renal agenesis or hypoplasia, whereas disturbances in quantitative development result in dysplasia, which is usually associated with the presence of cysts. Disruption of the normal embryologic migration of the kidneys results in renal ectopia (eg, pelvic kidney) and fusion anomalies (eg, horseshoe kidney). Patients with malformations with a reduction in kidney numbers or size are most likely to have a poor renal prognosis. Anomalies of the collecting system are associated with complete or partial duplication of the renal collecting system, ureteropelvic junction obstruction, abnormalities of the ureter such as megaureter, ectopic ureter, ureterocele, or vesicoureteral reflux, bladder extrophy, posterior urethral valves or other more rare sub-bladder obstructions. It has been noticed that anomalies of the collecting system are often associated with primary or secondary renal parenchymal changes.

Diagnosis or suspicion of a CAKUT is usually placed by the routine antenatal ultrasound. By 20th week of gestation fetal urine accounts more than 90% of the amniotic volume and by 25th week renal cortex and medulla are distinctly demonstrated. Counseling of families with fetuses with CAKUT should be available throughout the pregnancy and genetic amniocentesis may be discussed in certain cases. It has been reported a high sensitivity of an-
tenatal ultrasound screening for detecting renal malformations approaching 90% in certain cases at a mean gestational age of 23 week. In utero intervention may be discussed in selected limited number of rare cases with severe oligohydramnios due to obstructive uropathies.

Postnatal evaluation consisted of ultrasonography, routinely performed after 48 hours of life, except of severe cases, such as suspicion of posterior urethral valves, in which is performed within the first 24 hours. Further postnatal diagnostic procedures include evaluation of renal function and imaging studies selected separately for each case. Specifically, voiding cystourethrogram (VCUG) is indicated for detection of vesicoureteral reflux in patients with hydronephrosis and in male infants suspected for posterior urethral valves. Obstructive cases of hydronephrosis may be diagnosed and sent for surgical correction by 99mTc-mercaptotriglycglycine (MAG-3) renal scan. 99mTc-Dimercaptosuccinic acid (DMSA) is used to detect ectopic renal tissue, differential function between the two kidneys and renal dysplasia or scarring. During follow-up period serial ultrasounds are usually performed.

In general, children with CAKUT may have full, healthy lives. However, some children with renal agenesis, renal dysplasia complicated CAKUT or selected cases such as posterior urethral valves are at increased risk for developing chronic kidney disease (CKD) over time.

Inherited diseases

Based on clinical manifestations and family history, inheritance was suspected or accepted for a significant number of renal diseases. In 1980s genetics were first used in nephrology starting with mapping target genes of autosomal dominant polycystic kidney disease in 1985 followed in 1990 by the first identification of a causal mutation for Alport syndrome. Recently, the etiology of many kidney diseases have been revealed as single-gene defects. The degree of genetic causality varies with the mode of inheritance. Usually, molecular genetic diagnosis is used to clarify the etiology of a rare disease that is otherwise difficult to be diagnosed. Moreover, at least 10% of adults and nearly all children who progress to renal replacement therapy have an inherited kidney disease. With the increased use of high-throughput and next-generation sequencing technologies, has been defined the genetic basis of more than 160 rare kidney diseases. Considering nephron segments inherited disorders may be classified as glomerular, renal cystic and interstitial and tubular.

Inherited glomerular diseases

Single-gene glomerular diseases usually are presented with proteinuria and/or hematuria with dysmorphic red cells. They include congenital steroid resistant nephrotic syndrome ( Finnish type), other genetic forms of steroid resistant nephrotic syndrome causing defects in podocin, laminin-b, a-actinine-4 and phospholipase C production, Pierson syndrome, Denys-Drash syndrome, Frasier syndrome, Nail-Patella syndrome, Schimke immuno-osseous dystrophy, lysosomal disorders with steroid resistant nephrotic syndrome and Alport syndrome.

Inherited renal cystic and interstitial disorders

Inherited diseases may cause renal cystic and interstitial disorders. In these cases the main findings are ultrasonographic identification of renal cysts and increased echogenicity. Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent lethal dominant disease in the United States and Europe, affecting about 1 in 1,000 individuals. It is a multisystem disorder characterized by progressive cystic dilatation with variable extrarenal manifestations such as liver cysts and brain aneurysms. Most patients with ADPKD present renal cysts as adults or adolescents, however, some patients present cysts in early childhood and even, in rare cases, antenatal. It is very important the offsprings of the affected adults to be examined annually. Autosomal recessive polycystic kidney disease (ARPKD) is characterized by bilateral renal cystic enlargement that may start in utero. CKD develops directly postnatally, or in childhood or adolescence, depending on the severity of the two causative recessive mutations of gene PKHD1. Usually is associated with congenital hepatic fibrosis. In nephronophthisis, until recently have been recognized 9 types (types 1-9). Renal cysts are usually restricted to the corticomedullary border of the kidneys. The renal size is normal or even reduced in contrary with ADPKD and ARPKD. CKD mostly develops at a medium age of 13 years, with a range depending on disease type. Other inherited cystic disorders are Meckel-Gruber.
syndrome, medullary cystic kidney disease and Bardet-Biedl syndrome types 1-12\textsuperscript{29-31}.

**Inherited renal tubulopathies**

In inherited renal tubulopathies the primary genetic defect causes loss of function of a specific renal transport protein or signaling molecule. The leading diagnostic features are polyuria and abnormal renal tubular losses of electrolytes, sugar and amino acids, depending on the affected part of renal tubule. Disorders of the proximal tubule are characterized by inappropriate urinary loss of low-molecular-weight proteins such as β2-microglobulin and vitamin D-binding protein, aminoacids, glucose, phosphate, uric acid, and calcium and/or proximal renal tubular acidosis (RTA). Advances in molecular diagnostics have revealed that Bartter syndrome results from mutations in numerous genes that affect the function of ion channels and transporters that normally mediate transepithelial salt reabsorption in thick ascending limb of Henle’s loop the distal nephron segments, causing hypokalemic metabolic alkalosis. Defects of the distal convoluted tubule cause Gitelman syndrome and other forms of hypomagnesemia\textsuperscript{32-34}. Tubulopathies of the collecting duct impair reabsorption of water, sodium, potassium and protons, resulting in polyuria, salt loss, hyperkalemia, and acidosis, respectively. Mutations in the aquaporin-2 water channel AQP2 cause recessive nephrogenic diabetes insipidus (NDI), and mutations in the vasopressin-2-receptor cause X-linked NDI\textsuperscript{35-37}.

**Inherited diseases associated with nephrolithiasis and/or nephrocalcinosis**

Numerous rare single gene defects are associated with nephrolithiasis and/or nephrocalcinosis. Many of them represent rare abnormalities of specific renal tubular transport channels and transporter and account for approximately 2% of kidney stones in adults and 10% of childhood stones. A genetic disorder should always be considered during evaluation of kidney stones in children. Of high suspicion are cases of: early onset, positive family history, consanguineous parents, highly-active stone disease, renal hypercorticogenicity, tubular dysfunction and related manifestations, renal failure, extrarenal manifestations and particular stone composition such as crystalluria, monohydrate calcium oxalate, cystine dihydroxyadenine, xanthine. The most common single gene disorders associated with nephrolithiasis are cystinuria, primary hyperoxaluria, Dent’s disease and adenine phosphoribosyltransferase deficiency\textsuperscript{38}.

**Inherited diseases associated with renal tumors**

Multiple benign and malignant tumors of the kidney can be caused by single-gene defects\textsuperscript{39}. In table 3 are summarized the most common single-gene defects that associated with renal tumors.

**Table 3.** The most common single-gene defects associated with renal tumors

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Genes</th>
<th>Renal tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberous sclerosis types 1 and 2</td>
<td>TSC1, TSC2</td>
<td>Angiomyolipomas</td>
</tr>
<tr>
<td>Von-Hippel-Lindau disease</td>
<td>VHL</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Wilm’s-tumor-aniridia syndrome</td>
<td>WT1</td>
<td>Wilm’s-tumor</td>
</tr>
<tr>
<td>Papillary renal cell carcinoma</td>
<td>MET</td>
<td>Renal cell carcinoma</td>
</tr>
</tbody>
</table>

**Glomerular diseases**

**Acute post-streptococcal glomerulonephritis**

Acute post-streptococcal glomerulonephritis (APSGN) is the commonest cause of acute nephritis in children globally. It mainly occurs in developing countries and as of the estimated 470,000 new annual cases worldwide, 97% are recorded in regions with low socioeconomic status\textsuperscript{40}. It usually occurs 1-3 weeks after an episode of strep throat or a skin infection associated with specific nephritogenic strains of group A beta-hemolytic streptococcus. In epidemic cases APSGN may occur in 10% of children with pharyngitis and up to 25% of children with impetigo\textsuperscript{40,41}. The most effective public health measure in the developing world is to improve hygiene and provide better housing conditions to avoid overcrowding. This offers the best hope for elimination of epidemic pyoderma and thus preventing APSGN. Furthermore, APSGN is prevented by early antibiotic treatment, and the spread of nephritis-associated streptococcal infection is contained by prophylactic antibiotic treatment to individuals at risk. The challenge is to define who should be treated, as sometimes the diagnosis of
streptococcal infection is uncertain. The decision is straightforward with active skin infections because the differential diagnosis is between staphylococcal and streptococcal impetigo. In contrast, the diagnosis of streptococcal pharyngitis on clinical grounds alone is uncertain. Therefore, several clinical scoring systems have been developed to increase the accuracy of diagnosis for the prescription of antibiotics. 42

Generally, children have an excellent outcome with the majority showing complete recovery. Fewer than 1% of children have elevated serum creatinine values after 10-15 years of follow-up. 40, 41

**Nephrotic syndrome**

The main acquired conditions associated with nephrotic syndrome in children are minimal change nephrotic syndrome (MGNS), focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis. Minimal change nephrotic syndrome accounted for more than 90% of steroid sensitive nephrotic syndrome cases in children and present favorable outcome. However more than 60% of the patients present rare or frequent relapses throughout childhood. Focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis are usually presented as steroid resistant nephrotic syndrome in older children and adolescents. Addition of alkylating or other immunosuppressive agents in treatment may increase the response rate in children.

**Vascular and interstitial diseases**

**Hemolytic uremic syndrome**

The hemolytic uremic syndrome (HUS) is characterized by the triad of simultaneous presence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. It is one of the main causes of acute kidney injury in previously healthy children and accounts for a important number of pediatric patients who progress to end-stage renal disease. Although all pediatric cases exhibit the classic triad of findings, there are a number of various etiologies of HUS that result in differences in presentation, management, and outcome. HUS is classified into three categories: (i) typical disease ii) sporadic atypical cases that occur secondary to infections, medications, systemic diseases or malignancy and (iii) familial atypical cases predominantly due to genetic abnormalities of complement regulatory proteins. In all forms of HUS, there is evidence of both systemic and intra-glomerular inflammation and perturbations in the immune system. 43

Typical disease occurs sporadically or in epidemic outbreaks and is related mainly to infection with strains of *E. coli* producing Shiga toxins (STEC) or other microorganisms that elaborate Shiga toxin. Its incidence ranges from 6 per 100,000 in children under the age of 5 years to 1-2 per 100,000 in the overall population. 44 There are only few measures that could be taken to prevent STEC-HUS. It seems that adequate amounts of sodium-containing intravenous fluids during the prodromal phase may prevent activation of the coagulation cascade within the glomerular microcirculation and prevent progression of STEC enteritis to HUS. However there is no proven therapy for STEC-HUS that reduces the need for acute renal replacement therapy, shortens the course, or improves long-term outcomes. 44 It is very important the supportive management of acute kidney injury, anemia, hypertension, fluid-electrolyte imbalances and on time initiation of renal replacement therapy. The agent that has received the most attention recently as a potential treatment for STEC-HUS is eculizumab, a monoclonal antibody to C5a. Most recent studies are case series and a randomized clinical trial is needed to define the place of eculizumab in the management of STEC-HUS. 45

Considering atypical HUS (aHUS), following FDA approval in September 2011, treatment with eculizumab has become the standard of care for all these patients. Reports have shown that treatment with eculizumab in patients with aHUS and renal damage resulted in a significant increase in platelet count and achievement of a relapses free status in 80% of cases. 46 However a high relapse rate is described in cases of discontinuation. 47 Patients with genetic forms of aHUS and unsuspected disease activity may demonstrate clinical improvement after switching from plasma therapy to eculizumab treatment. 48 Finally, eculizumab enables successful kidney transplantation in those who progress to ESKD. 49

**Tubular-interstitial nephritis**

Patients with acute tubular-interstitial nephritis (TIN) may present with nonspecific signs and symptoms of acute renal dysfunction. These may include
the acute or subacute onset of nausea, vomiting, and malaise. However, many patients are asymptomatic. Patients may be oliguric in 51%, present gross hematuria in approximately 5% and usually do not have significant proteinuria. Classically, patients with drug-induced AIN were reported to have symptoms and/or signs of an allergic-type reaction, including rash, fever, and eosinophilia. However, only 10% of patients presented the characteristic triad. In children drugs are the most common cause of TIN including nonsteroidal anti-inflammatory, penicillins and cephalosporins, rifampin, antimicrobial sulfonamides, ciprofloxacin and other quinolones, diuretics, cimetidine, allopurinol, proton pump inhibitors, indinavir, 5-aminosalicylates (e.g., mesalamine) and many other drugs. Drug-induced AIN should be suspected when the onset of characteristic laboratory findings are temporally related to the initiation of a new drug, particularly one that has been previously reported to cause TIN. Autoimmune disorders have also been associated with TIN. A definitive diagnosis of AIN is made by renal biopsy. There is no definitive evidence that corticosteroid therapy is beneficial. However, a course of prednisone may be considered in some patients.

Systemic diseases

Henoch-Schönlein purpura nephritis

Henoch-Schönlein purpura (HSP) is the most common vasculitis in children. Disease prognosis is mostly dependent upon the severity of renal involvement. Nephritis is observed in about 30% of children with HSP and may lead to chronic kidney disease in up to 20% of children with HSP nephritis in tertiary care centers, but in less than 5% of unselected patients with HSP, by 20 years after diagnosis. Severity and/or duration of extrarenal HSP symptoms and an older age are the most significant risk factors for developing HSP nephritis (HSPN). As clinical and histological severity at nephritis onset are in general predictive of a long-term renal impairment. The existing evidence does not support of short course prednisone in preventing persistent renal disease in children with HSP. For the treatment of severe HSPN, aggressive therapies including multiple drug combination therapy and plasmapheresis have been shown to be effective in ameliorating proteinuria and histological severity. Nevertheless, detailed investigation into the pathogenesis of HSPN and double-blind randomized control studies on children with HSPN are still necessary.

Lupus Nephritis

About 20% of systemic lupus erythematosus (SLE) starts in childhood and children have less gender bias in favor of females as compared to adults. Renal disease occurs in 50% to 75% of all childhood SLE (cSLE) patients, mostly within the first 2 years after diagnosis. Initial manifestations of renal disease range from minimal proteinuria and microscopic hematuria to nephrotic-range proteinuria, urinary casts, severe hypertension, peripheral edema, and renal insufficiency or acute renal failure. SLE most commonly affects the glomerulus, but can also involve the renal interstitium. It can also present with features of thrombotic microangiopathy including both atypical hemolytic uremic syndrome as well as thrombotic thrombocytopenic purpura.

Since most children develop lupus in their early adolescence, dealing with the diagnosis of an unpredictable lifelong disease during this phase of life is challenging. Steroids and immunosuppressive drugs are the cornerstone for treatment in children with lupus nephritis. The outcome has improved considerably with these drugs and 10-year survival is nearly 90%. However it have been noticed that mortality related to SLE nephritis has been static over the last decade. Hence, there is a strong need for more effective drugs with, if possible, fewer side-effects.
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Conflict of interest statement
None declared

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