Review Article

http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v8i3.31147

Chronic Kidney Disease in Children: A Review

Mohd Ashraf[1]*
Muzafar Jan[2],
Khurshid Ahmed Wani[2],
Parvez Ahmed[2],
Javid Ahmed[3],
Sheikh Nisar Ahmed[4]

[1]Lecturer Pediatric Nephrology, Department of Pediatrics, Govt Medical College, Srinagar, Jammu and Kashmir, India.
[2]Professor, Department of Pediatrics, Govt Medical College, Srinagar, Jammu and Kashmir, India.
[3]Associate Professor, Department of Community Medicine, SKIMS Soura, Srinagar, Jammu and Kashmir, India.
[4]Post Graduate Scholar, Department of Pediatrics, Govt Medical College, Srinagar, Jammu and Kashmir, India.

*Corresponding Author
Mohd Ashraf, MD
Email: aashraf05@gmail.com

Received: June, 2020
Revised: June, 2020
Accepted: August, 2020

Abstract

Chronic kidney disease (CKD) in children is a life-consuming ailment with a variable but progressive course. CKD, in particular, the end stage kidney disease (ESKD) affects multiple body systems complexed with secondary complications that significantly and adversely affect the growth, development and quality of life. Although uncommon in children, CKD poses unique challenges to the health care delivery system to manage the primary renal disorders and extrarenal manifestations of CKD along with a heavy socioeconomic burden. Despite the availability of better management tools, there is a rise in incidence and prevalence of pediatric CKD for which wide range short- and long-term planning is inevitable that will lure the medicos to acquire the advanced nephrological training and skills, besides providing quality infrastructure and sustained socio-economic support. Our review is aimed to provide recent advances regarding the evaluation and management of pediatric CKD and its complications.

Keywords: Anemia; Children; End stage kidney disease; Epidemiology; Growth; Mineral and bone.

Conflict of interest: The author declares no conflict of interest.
Please cite this article as: Ashraf M, Jan M, Wani KA, Ahmed P, Ahmed J, Ahmed SN. Chronic Kidney Disease in Children: A Review. J Ped Nephrol 2020;8(4):1-9.
https://doi.org/10.22037/jpn.v8i3.31147

Introduction

Chronic kidney disease (CKD) is the serious clinical syndrome characterized by gradual and irreversible loss of renal function (1). With the global rise of its incidence and prevalence, chronic kidney disease (CKD) in children is emerging as a major public health problem with far reaching socioeconomic and public health consequences (2,3). In adults CKD is usually caused by diabetes and hypertension, while pediatric CKD is mostly due to congenital anomalies of the genitourinary system and glomerulopathies, however both in adults and children, common denominator remains its progression to end stage renal disease which is uniformly fatal without renal replacement therapy.

Although CKD in children is uncommon (4), however, it presents with a higher cost perindividual than adult CKD care (5), and carry with it unique challenges.

To overcome these unique challenges, Kidney Disease: Improving Global Outcomes (KDIDO) (1), devised a classification system based on cause of kidney disease, glomerular filtration rate (GFR) and albuminuria category (CGA). Following on similar classification system in pediatric CKD, it was observed that the combined GFR, proteinuria, and CKD diagnosis is more predictive for estimating the risk of disease progression in pediatric CKD patients than GFR alone (6).

Epidemiology

As per the estimates of Global Burden of Disease study in 2015, more than 750 million persons suffer from CKD (7), and about 1.2 million people died of CKD (8). Although there is robust and extensive epidemiological data available in adult population, but there is paucity of similar data about pediatric CKD and ESKD (4,9). National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002, published guidelines on evaluation and management of CKD, applicable to both adult and pediatric population (10). This was followed by availability of quality pediatric CKD epidemiologic outcome data which helped the KDIGO to update the CKD classification system in 2012, for both adult and pediatric CKD patients; that superseded the previous CKD definitions (11). In some major prospective pediatric CKD studies like ItalKid Project and North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS); CKD was defined a glomerular filtration rate (GFR) of below 75 ml/min/1.73 m^2 (12,13).

Due to absence of a uniform definition of CKD and a well-defined classification of its severity, the majority of studies were based on data obtained from moderate to severe CKD or ESKD patients (14). As per European data, an incidence of pediatric CKD is about 11–12 per million of age-related population (pmarp) for CKD stages 3–5, while the prevalence is~55–60 pmarp (4). In USA, National Health and Nutrition and Examination Survey data from 1999 to 2006 estimated the incidence of pediatric CKD about 82 cases per million per year, and incidence of ESKD, about 15 cases per million per year (15). With the established fact of rising incidence and prevalence of CKD (16), patients with earlier stages of the disease are likely to exceed 50 times than that of ESKD patients (17). By definition (1), CKD is the presence of any structural or functional abnormality of kidneys in the form of pathologic, laboratory or imaging findings for ≥3 months or a GFR <90 ml/min/1.73 m2 for ≥3 months. However, it is not applicable to new-borns or infants <3 months of age, < 2years where GFR <90 ml/min/1.73 m^2, albuminuria ≥30 mg/24 h, and all electrolyte abnormalities.

Etiology

In adults, diabetes followed by hypertension are the leading causes of CKD, while in children, congenital anomalies of the kidney and urinary tract (CAKUT) followed by glomerulopathies are common causes of CKD (18,19). Uncommon causes of pediatric CKD include hemolytic uremic syndrome, nephrolithiasis/nephrocalcinosis, Wilms tumor, infectious and interstitial diseases, and others (19).

With the advent of next-generation sequencing (NGS) substantial clues are unravelling the etiology of early onset CKD, especially a significant proportion ~20% of cases of CKD before 25 years of age are monogenic CKD. Approximately more than 200 genes have been identified as causative of CAKUT, SRNS, chronic glomerulonephritis and ciliopathies (20, 21). It is heartening that by precise genetic panel sequencing based on the clinical/laboratory features, it seems possible that in one-fifth of children with early-onset CKD can be appropriately managed (18). Overall, either in general or individually a recognized genetic cause of pediatric onset of CKD might benefit from specific therapies or from the avoidance of ineffective and even potentially harmful ones. Causes of pediatric CKD are detailed in Table 1 (22).

Clinical spectrum

Pediatric CKD is suspected clinically either through typical clinical syndrome or with isolated clinical feature in the form of short stature, poor appetite, growth failure, anemia, bone deformities, generalized fatigue, lack of energy, edema, seizures, dyspnea, hearing loss, recurrent infections or through routine screening with urine, serum chemistry, or imaging of genitourinary system. At times patients may present with symptoms of gross hematuria, flank pain, low urine output, persistent pyuria, polyuria, incontinence, poor urine stream, urgency and nocturia. A detailed history, right from fetal period including oligohydramnios, polyhydramnios, hydronephrosis, fetal imaging abnormalities, perinatal events, urinary tract infections along with the bowel and bladder related issues should be sought. In addition, a family history of kidney diseases, sickle cell trait (23), nephrolithiasis or recurrent urinary tract infections, autoimmune disease, presence of hypertension (24), or, diabetes (25), has to be looked for. Thorough physical examination with predominant focus on blood pressure, anthropometry, growth velocity,

Table 1. Causes of CKD from various studies

Study name	NAPRTCS	Italian Registry	Belgian Registry	Nigeria	Serbian Registry	Turkish Study	British Study	Japanese Study
CKD Stage	CKD 2-5 (GFR <75)	CKD 2-5 (GFR <75)	CKD 3-5 (GFR <60)	CKD 3-5	CKD 2-5 (GFR <90)	CKD 2-5 (GFR <75)	CKD (GFR <60)	CKD 3-5
Age (years)	0–20	0–19	0–19	0–16	0–18	0–18	0–17	0—15
Patients	Registered 1994-2007	Incident 19900-2000	Incident 2001-2005	Incident 2007-2012	Incident 2000-2009	Incident 2005	Incident 2005-2009	Prevalent 2010
Number of cases	7037	1197	143	98	336	282	288	447
Etiology								
CAKUT	3361 (48 %)	689 (58 %)	84 (59 %)	19 (19 %)	160 (58 %)	163 (58 %)	170 (59 %)	278 (62 %)
Hypodysplasia ± reflux nephropathy	1907	516	66	-	-	120	127	218
Glomerulonephritis	993 (14 %)	55 (5 %)	10 (7 %)	56 (57 %)	40 (12 %)	41 (15 %)	36 (13 %)	21 (5 %)
HUS	141 (2 %)	43 (4 %)	9 (6 %)	-	-	05 (2 %)	10 (3 %)	4 (1 %)
Hereditary nephropathy	717 (10 %)	186 (15 %)	27 (19 %)	-	49 (15 %)	49 (17 %)	40 (14 %)	62 (14 %)
Congenital NS	75	13	5	-	-	-	4	3
Metabolic disease	-	-	5	-	-	14	16	-
Cystinosis	104	22	2	-	-	4	11	1
Cystic kidney	368 (5 %)	101 (8 %)	13 (9 %)	-	-	35 (12 %)	16 (6 %)	39 (9 %)
Ischemic renal failure	158 (2 %)	49 (4 %)	3 (2 %)	-	-	-	12 (4 %)	40 (9 %)
Miscellaneous	1485 (21 %)	122 (10 %)	10 (7 %)	14 (14 %)	48 (14 %)	-	13 (5 %)	37 (8 %)
Missing/Unknown	182(3%),	40(3%)	-	8(8.2%)	6(2%)	22(8%)	7(2%)	5(1%)

CAKUT: congenital anomalies of the kidney and urinary tract, NS nephrotic syndrome, HUS hemolytic uremic syndrome
Adopted from van Stralen KJ, Harambat J, Clayton P, Crai JC. Demographics of CKD and ESRD in Children. In: Pediatric Kidney Disease. Denis F. Geary Franz Schaefer (Eds), 2nd Edition. Springer-Verlag Berlin Heidelberg 2016; pp 1387

skeletal deformities, dysmorphism, developmental and psychological issues can provide very important clues regarding the likely underlying illness. Flank fullness or pain may suggest enlarged kidneys, hydronephrosis, obstructive uropathy, nephrolithiasis, pyelonephritis, or polycystic kidney disease. Patterned skin rashes as in systemic lupus erythematosus, acute interstitial nephritis, Henoch-Schoenlein purpura, cryoglobulinemia, vasculitis, telangiectasia as in scleroderma, Fabry disease may prove very helpful. Volume depletion or overload may be present in poor oral intake, vomiting, diarrhea, or diuresis, nephrotic syndrome, SIADH, decompensated heart failure, liver failure. Fundus examination may reveal the presence of arterial-venous nicking suggestive of long-standing hypertension or diabetes. Patients with carotid or abdominal bruits may have renovascular disease.

Nutrition

Children with CKD and ESKD do have protein-energy wasting, causes of which include reduced intake, recurrent vomiting, anorexia and feeding problems (26). Children with CKD frequently develop gastroesophageal reflux, which contributes to reduced nutritional intake and abnormal secretion and destruction of gut peptides that cause dysregulated motility, and hunger (27,28). Due to multiple factors involved in Pediatric CKD, like age, gender, nutritional status, CKD stage, and growth patterns, the diet must include appropriate amount of calories, protein, sodium, potassium, calcium, phosphorus, and iron; a comprehensive balanced nutrition that may require supplements to attain the required proteins and calories is the key for proper growth and development (29,30). The goal is to generally provide energy requirements at 100% of the recommended daily allowance (RDA) for age, some children who need catch-up growth may require energy intake at 120–140% of the RDA (31). The current KDOQI guideline (32), recommend supplying 100–140% of the dietary reference intake (DRI) of protein for ideal body weight for children with stage 2–3 CKD. However, those receiving peritoneal dialysis may require further supplementation.

Growth and development

Maintaining normal growth and development is one of the most critical issue in the management of Pediatric CKD. More than one third of pediatric CKD patients have growth impairment before reaching ESKD, along with serious psychosocial issues (33,34). Linear growth impairment affects the quality of life, self-esteem, social adjustment and is associated with higher mortality (35). Growth

failure in pediatric CKD results from the interplay of multiple factors that originates from the fetal period as intrauterine growth restriction, inadequate nutrition, electrolyte disturbances, disturbances of the somatotropic and gonadotropic hormones, mineral and bone disorder (MBD), and metabolic acidosis (36-38). Growth of an infant is predominantly under nutritional influence, while in childhood growth is dependent on optimal levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I) (39); so a combination of loss of appetite, recurrent vomiting along with GH and its mediator deficiencies will result in growth impairment (40). Consensus paper guideline on the use of recombinant human growth hormone (rhGH), recommends that pediatric CKD stage 3-5, or who are on dialysis should receive GH therapy if they have persistent growth failure, provided potentially treatable risk factors for growth failure are corrected first; while post-transplant should receive GH therapy 1 year after transplantation if spontaneous catch- up growth does not occur and steroid-free immunosuppression is not a feasible (41).

Mineral and Bone Disease

CKD bone and mineral disease (CKD-MBD) is one of the most common complications of CKD, characterized by the presence of one or a combination of the following findings: abnormalities in calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), or vitamin D metabolism; alterations of bone turnover, mineralization, elongation and strength, extra skeletal calcification or abnormalities in bone histology (42). Due to tight regulation of serum calcium and phosphorus in early stages of CKD, that keeps them normal; however, the levels of FGF-23 are already high, even before the presence of clinical spectrum as has been shown from the multicenter CKiD (Italkid) study (43).

Persistently high levels of FGF 23, in later stages of pediatric CKD results in secondary hyperparathyroidism, partly because of Klatho receptor insensitively and decreases renal synthesis of active Vitamin D. This complex interplay results in disordered bone and mineral metabolism, that needs an effective management to reduce the progression of cardiovascular disease (CVD), a leading cause of death among the pediatric CKD patients (44,45).

Current guidelines for CKD-MBD management, recommend strict control of hyperphosphatemia, avoid positive calcium balance and correction of secondary hyperparathyroidism, to achieve the goal of quality bone and prevention of vascular calcification. Nevertheless, many patients do poorly with mineral and bone metabolism that too in later stages of CKD, a trend which has been observed in an International Pediatric Peritoneal Dialysis Network on 900 children globally, where in ~50% of the patients, had PTH levels over five times above the upper limit and highest levels were observed with higher phosphate and lower calcium levels. Dietary management of CKD-MBD include dietary phosphorus restriction in cases of hyperphosphatemia and hyperparathyroidism to 80% of the DRI for age (29), while KDOQI guidelines recommend limiting age specific phosphorus intake to 100% of the DRI (32). Human milk is low in phosphorus and is recommended in infantile CKD, in absence of which a low-phosphorus formula is recommended. Both breast milk and formulas can be pretreated with sevelamer to reduce the phosphorus absorption (46). Pediatric CKD patients should be offered fruits, vegetables, corn and rice, which are low-phosphorus, however, a caution must be exercised to avoid the occurrence of protein energy wasting, as most of the high quality protein and energy foods are rich in phosphorus.

Metabolic Acidosis

Metabolic Acidosis (serum bicarbonate <22 mmol/l), is present in approximately 20% of adult patients with advanced CKD (47), and 18% among the pediatric CKD patients with GFR> 50mL/min/1.73 m^2 (48). Metabolic acidosis results in the decreased capability of ammonia generation, reclaiming filtered bicarbonate, and excretion of hydrogen ions (37). During earlier stages of CKD, a normal anion gap metabolic acidosis is the frequent occurrence while high anion gap metabolic acidosis is seen in advanced CKD, as the kidney cannot excrete organic acids, leading to overwhelming of circulating buffers with subsequent release of calcium from bone, which leads to osteopenia, growth impairment, secondary hyperparathyroidism (49).

CKD induced metabolic acidosis impairs the protein and muscle metabolism, stimulates inflammation, and enhances insulin resistance. An

association between serum bicarbonate and adverse renal outcomes like progression to end-stage renal disease (ESRD) and mortality has been well established (50,51), and an indirect evidence that renal tubular acidosis may be a contributory factor of poor growth in children with CKD (52) Control of metabolic acidosis may retard CKD progression, secondary hyperparathyroidism, muscle weakness and malnutrition (53-55).

Anemia

Anemia (decrease in either the number or quality of red blood cells) is one of the common manifestations of CKD. According to data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), the prevalence of anemia in children is 73% at CKD stage III, 87% at stage IV and >93% at stage V (56), which is a predictive indicative of increased prevalence of anemia with the advancement of CKD. Anemia is contributory in poor quality of life, neurocognition, cardiovascular disease, exercise tolerance, sleep and appetite (57-59). Anemia of CKD is primarily due to erythropoietin deficiency, however, other contributing factors include iron deficiency, malnutrition, inflammation, uncontrolled hyperparathyroidism, blood loss, bone marrow suppression or ongoing systemic diseases (60). With the advent of erythropoiesis stimulating agents (ESA) the management of anemia of CKD was revolutionized. However, endogenous erythropoietin and ESAs are effective only when iron is readily available for erythropoiesis. Hepcidin a hepatic hormone is elevated in CKD patients, that bind with the ferroportin and impairs the iron egress, makes it less available for hemoglobin synthesis and decreases the iron absorption from gut that finally leads to disruption in iron metabolism (61). It is assumed that hepcidin excess precedes erythropoietin dysfunction as reflected by a much higher prevalence of iron therapy in children with mild to moderate CKD than ESA therapy and there are apprehensions about iron overload and toxicity in CKD (62,63). Hemoglobin concentration is <13.5 g/dL in men and <12 g/dLin women (64) is anemia of CKD in adults, while in children the diagnosis is based on the normative data where evaluation of anemia is warranted when age and gender specific hemoglobin levels fall below the 5th percentile (65,66). Both in adults and children level of hemoglobin must be approximately 11 g/dL or slightly greater, and levels >13 g/dL are not associated with improved patient outcomes (64). Iron supplementation with a starting dose of 3– 4 mg/kg/day of elemental iron with periodic assessment of iron levels is mandatory in pediatric CKD (67).

In children administration of recombinant human erythropoietin rHuEPO) is safe and effective, starting at 275 U/kg to 350 U/kg per week for infant and 200-250 U/kg/week for older children (68,69).

Cardiovascular disease

Cardiovascular disease (CVD) in children, adolescents, and young adults with CKD is the most important comorbidity affecting long-term survival (70). The prevalence of cardiovascular events in children ages 0 to 4 years and 15 to19 years with ESRD is 24.3% and 36.9% respectively (60). Previous studies have shown that pediatric CKD patients with CVD, carry one thousand times higher risk of mortality in the ESKD group as compared to general population (71,72).

It is well recognized that cardiovascular changes start early in the course of CKD, irrespective of the modifiable and non-modifiable risk factors (71,73), Combination of risk factors like blood glucose dysregulation, obesity, hypertension, dyslipidemia, increased calcium-phosphorus product, anemia and hyperparathyroidism play significant role in development of CVD in pediatric CKD (70). Cardiovascular death in pediatric CKD are due to arrhythmias, cerebrovascular disease, acute myocardial infarction, valve diseases, cardiomyopathy, cardiac arrest, pericarditis and congestive heart failure/pulmonary edema (44,70). It is well established that non-occlusive arterial stiffening in pediatric ESRD is more often due to medial calcification and is strongly associated uremia (75), furthermore, most pediatric studies evaluating LV structure have consistently shown that LVH develops even when CKD is mild and progresses with advancement of CKD (75,76) LVH may contribute initially to diastolic dysfunction followed by systolic dysfunction and cardiac failure, in addition to conduction disturbances of the myocardium that can cause arrhythmias (72).

Sodium

Sodium is an important electrolyte for neuronal growth and development (32,77), and may be used as supplementation in various obstructive

uropathies and/or renal dysplasia that are associated with excessive urine sodium loss, while CKD resulting from glomerular diseases and advanced CKD on dialysis require sodium restriction (78), to optimize the blood pressure. Research has shown that chronic total body sodium deficit may contribute to growth impairment (79), which implies a cautious approach be taken to optimize sodium intake in pediatric CKD.

Potassium

With the progression of CKD, potassium is retained due to progressive nephron loss, that poses a threat for arrhythmias and higher mortality (80,81).

Other contributory factors leading to hyperkalemia in pediatric CKD are urinary obstruction, rhabdomyolysis, hemolysis, acidosis, treatment with potassium-sparing diuretics, ACE-inhibitors and angiotensin receptor blockers, calcineurin inhibitors, and NSAIDS (82) KDOQI guidelines suggest that pediatric CKD patients should restrict potassium of 30–40 mg/kg/day (0.8–1 mmol/kg/day) for older children, and 40–120 mg/kg/day for infants and younger children, for which breast milk and renal infant formulas can be used.

High potassium foods like banana, oranges, potatoes, tomatoes, lentils, yogurt, chocolate and legumes should be restricted. When dietary changes and/or potassium binders are not sufficient to correct hyperkalemia, non-dietary causes should be investigated which include hemolysis, hyperglycemia, constipation, acidosis, drugs, tissue breakdown and dialysis related issues.

Hypertension

Hypertension is one of the major risk factor for pediatric CKD progression (83), and this can be there even at the earliest stages of CKD. In fact, results from the CKiD revealed that hypertension was present in 54% of patients just at enrolment and 48% of the children had high blood pressure while on antihypertensive medications (84). In the ESCAPE trial of 385 children with CKD; patients with tight BP control (<50th percentile) had a 35% reduction in relative risk of GFR decline to 50% as compared with those in the conventional BP control group (85).

In general, most of the recent data demonstrates that pediatric CKD patients are underdiagnosed and have under controlled hypertension, where a heightened awareness regarding the early diagnosis and tight control of hypertension among pediatric CKD patients is the key to slow the progression of CKD.

Dyslipidemia

Dyslipidemia is well recognized risk factor for atherosclerosis both in adults and pediatric CKD patients. Various studies have demonstrated that the degree of dyslipidemia correlates with the degree of renal functional deterioration (86,87). In one of the major pediatric CKD study, a 45% prevalence of dyslipidemia was observed, a consistent pattern with data from adult CKD patients (88). Overall atherosclerosis begins during early life in general and dyslipidemia is the risk factor for its development (89). Dyslipidemia in pediatric CKD is possibly due to impaired TG lipolysis, associated with increased Apolipoprotein C-III and reduced insulin sensitivity in the vascular endothelium of skeletal muscle and other major sites of TG energy utilization (90). Dyslipidemia being a marker of CVD risk, with subsequent mortality; reducing lipid levels and obesity prevention could decrease CVD in pediatric CKD patients. Pediatric CKD dyslipidemia management guidelines suggest clinical benefit in initiating lipid-lowering therapy in selected older or higher-risk adults with non-dialysis CKD. No recommendation to treat dyslipidemia in children and younger adults with lower risk (91), which probably stems from insufficient data regarding benefit and harm. In this population, management of dyslipidemia should include nutrition and dietary counseling, stress on obesity management and weight loss wherever necessary.

Conclusion

Pediatric CKD is an irreversible progressive damage to the kidneys leading to high morbidity, mortality and poor quality of life. Life expectancy for a child on renal replacement therapy (RRT) is 50 years less than a normally growing child. Although less common in children, advanced CKD stages are associated with unique challenges requiring multidisciplinary team approach from dedicated pediatric nephrologists, pediatricians, together with allied specialists, renal dietician, family, and financial support agencies. Timely diagnosis and early intervention in the form proper management of hypertension, anemia, electrolyte disturbances,

metabolic acidosis, AKI, dyslipidemia and obesity along with provision of balanced nutrition can slow the CKD progression, improve quality of life, and may provide lead time for preparing the patient and family for better mode of RRT.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Support

Not declared.

Acknowledgement

Dr Vaseem Yousuf, Ainul Saba, Buruj Khattab and Jalees Khattab for their affectionate support during the preparation of this review.

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