Chronic kidney disease in children

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Abstract

Chronic kidney disease (CKD) is a major health problem worldwide. Although relatively uncommon in children, it can be a devastating illness with many long-term consequences. CKD presents unique features in childhood and may be considered, at least in part, as a stand-alone nosologic entity. Moreover, some typical features of paediatric CKD, such as the disease aetiology or cardiovascular complications, will not only influence the child’s health, but also have long-term impact on the life of the adult that they will become. In this review we will focus on the unique issues of paediatric CKD, in terms of aetiology, clinical features and treatment. In addition, we will discuss factors related to CKD that start during childhood and require appropriate treatments in order to optimize health outcomes and transition to nephrologist management in adult life.

Key words: chronic renal failure, chronic renal insufficiency, CKD, ESRD, paediatrics

Introduction

Chronic kidney disease (CKD) is a major health problem worldwide with increasing incidence and prevalence that is threatening to bring on the onset of a real ‘epidemic’ [1–5]. Independent of the initial cause, CKD is a clinical syndrome characterized by a gradual loss of kidney function over time [6]. In particular, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have defined CKD as abnormalities of kidney structure or function, present for more than 3 months, with implications to health [6]. This definition has been formulated for the adult population, where CKD is a common and well-known health problem, but the KDIGO guidelines for definition and staging are not fully applicable to the paediatric population [6]. Indeed, paediatric CKD, while sharing the basic physiopathologic mechanisms with the same disease in the adult population, could be in some ways considered a stand-alone nosologic entity. Childhood CKD presents clinical features that are specific and totally peculiar to the paediatric age, such as the impact of the disease on growth. In addition, some of the typical characteristics of paediatric CKD, such as the aetiology or cardiovascular complications, represent variables, not only influencing the health of the patient during childhood, but also having an impact on the life of the adult that this child will become. This impact is often under-recognized but should not be neglected. Moreover, CKD has a great psychosocial impact, both on the patient and his family. The parents not only have to fulfill the role of parents, but also take on many tasks we normally associate with nurses and doctors. Therefore, we must be aware that the increasing survival of paediatric patients with CKD, due to the improvement in the clinical and therapeutic management, will lead to a large number of affected adults facing problems that are specific to CKD that have started during childhood.

In this review, we will focus not only on the unique issues concerning paediatric CKD, but especially on those factors related to...
CKD that start during childhood and require appropriate management to optimize health outcomes of the patient.

**Epidemiology of CKD in children**

According to the KDIGO guidelines, CKD is identified by the presence of kidney damage, either structural or functional, or by a decline in glomerular filtration rate (GFR) below 60 mL/min/1.73 m² of body surface area for more than 3 months [6]. Therefore, the term CKD defines renal dysfunction as a continuum, rather than a discrete change in renal function, either in children or in adults [7]. This makes the epidemiology of CKD very difficult to study. Moreover, epidemiologic data on CKD may underestimate its real incidence and prevalence since CKD is often clinically asymptomatic, especially in earlier stages [8]. This is in part the result of the historical absence of a common definition of CKD and of a well-defined classification of its severity [9], that have recently, at least in part, been overcome by the introduction of the KDIGO guidelines [6, 9]. For all these reasons, in the majority of studies, estimates of CKD take into account patients with moderate to severe CKD or end-stage renal disease (ESRD) and are not population-based in nature [8, 9]. In addition, childhood CKD registries are usually limited by being restricted to small reference populations [10]. Despite these limitations, the paediatric incidence of CKD in Europe is reported to be around 11–12 per million of age-related population (pmarp) for stages 3–5, while the prevalence is ~55–60 pmarp (Figure 1, top) [11, 12, 13, 17]. Comparable amounts are reported in population-based registries of other western countries [14], although no precise data on the incidence and prevalence of pre-terminal CKD are available for the majority of them (Figure 1, top) [9]. Some differences could emerge if different age groups are analysed [10, 18]. The incidence of paediatric CKD rose slowly during the 1980s, then marginally until the first decade of the 21st century [19]. At the same time, the prevalence of the disease has significantly increased since survival and treatment of CKD have markedly improved [20]. Specific reports on CKD epidemiology in children have been focused on patients with ESRD requiring renal replacement therapy (RRT). The median incidence of RRT in children <20 years old is ~9 pmarp worldwide, whereas the prevalence is reported as ~65 pmarp (Figure 1, bottom) [9, 13, 21]. Moreover, higher values for incidence and prevalence have been reported in the USA, probably because RRT is started earlier, at higher levels of GFR, in comparison with other developed countries [15]. In any case, data coming from epidemiological studies in adults provide the dramatic evidence that ESRD represents the ‘tip of the iceberg’ of CKD and suggest that the number patients with earlier stages of the disease are likely to exceed those reaching ESRD by as much as 50 times [22]. The same consideration could probably be applied to the paediatric population, where CKD has only recently been recognized as a non-marginal issue. Notably, 80% of RRT in children is performed in Europe, Japan and North America, where the cost of these extremely expensive treatments can be afforded [9]. As a consequence, the real impact of CKD in children in developing countries is a long way from being clarified, especially in those countries where the healthcare resource allocation to RRT is inadequate or RRT is not available, and children affected by CKD frequently die [9, 23, 24].

The incidence and prevalence of CKD is greater in males than females because of the higher frequency of congenital abnormalities of the kidney and urinary tract (CAKUT) in males [11]. Finally, race is another factor specifically affecting the epidemiology of CKD. In particular, in North America, the incidence of CKD is two to three times higher in African-American children compared with Caucasian children, irrespective of gender [14], whereas in Australia and New Zealand, the risk of ESRD is greater in indigenous children (e.g. Aborigines and Maoris) than in the remainder of the paediatric population [25].

**Aetiology of CKD in children**

Primary causes of CKD in children significantly differ from those that are responsible for the adult onset of the disease. In fact, the main aetiologic factors of CKD in children are represented by CAKUT, steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis (e.g. lupus nephritis, Alport syndrome) and renal ciliopathies, that account for approximately 49.1, 10.4, 8.1 and 5.3% of cases, respectively [11, 26, 27] and for more than 70% of all paediatric CKD cases when considered together, as recently reported (Table 1) [26]. Less common causes of CKD in children include thrombotic microangiopathies (especially atypical haemolytic uraemic syndrome), nephrolithiasis/nephrocalcinosis, Wilms tumour, infectious and interstitial diseases, and others (Table 1) [26]. While structural causes (e.g. renal hypoplasia or posterior urethral valves) clearly predominate in younger patients, the incidence of glomerulonephritis increases in those >12 years old (Figure 2) [9, 26]. However, minor reductions in nephron numbers that are seen in low-birth weight and small for gestational age newborns are now emerging as important predisposing factors to CKD and will come to represent an important issue for nephrologists as the number of premature children continues to grow [28–31]. These conditions, together with the exploding burden of paediatric obesity [32, 33], are probably destined to significantly change the relative distribution of the causes of CKD.

Interestingly enough, if analysis of the causes is limited to the population of children that have already reached ESRD, the relative percentage of glomerular diseases increases (approximately doubling), whereas that of CAKUT decreases from around 50 to 39.5%, underscoring the discrepancy between the rate of progression of these two entities (Table 1). Indeed, congenital malformative disorders are characterized by a slower progression towards ESRD in comparison with glomerular diseases so that, as mentioned before, the relative proportion of glomerular diseases increases in groups of patients with more advanced stages of CKD (Table 1) [9]. Somewhat different are the data from the Japanese National registry and the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry, which reported glomerulonephritis to be the most common cause of ESRD in children and adolescents [16, 34]. Finally, although information on the aetiology of ESRD from less-developed countries is almost unavailable mainly due to the absence of renal registries, it is reasonable to state that the burden of glomerulonephritis secondary to infectious diseases (such as hepatitis C, tuberculosis, HIV) is predominant and still far from being under control [9].

The recent advent of massive-parallel sequencing technologies (also referred to as next-generation sequencing, NGS) has provided one of the most interesting and substantial clues in unravelling the aetiology of early-onset CKD. In particular, studies performed over the past few years have demonstrated that a significant proportion of cases of CKD manifesting before 25 years of age can be defined as monogenic. In other words, a single gene can be detected as the cause of the disease in ~20% of early-onset patients [26]. Nowadays, more than 200 genes are clearly recognized as causative of the most common aetiologic categories of CKD in children (CAKUT, SRNS, chronic glomerulonephritis and ciliopathies) [26, 35, 36]. NGS technology presents the striking advantage of allowing us to simultaneously study an elevated number of genes in a single run of sequencing, saving
both time and costs while being extremely highly informative. Therefore, by selecting an appropriate panel of genes to sequence on the basis of the clinical phenotype of the patient or on a precise diagnostic suspicion, it is possible to address specific aetiological questions in one-fifth of children with early-onset CKD [26]. In addition, large population-based genetic studies (e.g. genome-wide association studies) are revealing that the genetic background of patients with CKD is probably much more complex than what was previously expected. Indeed, besides clearly disease-causing genes, that are by themselves responsible for disease determination, a number of other genes are now recognized as playing an important role [26, 37]. The best known example is represented by APOL1, whose variants confer a considerably higher risk of developing focal segmental glomerulosclerosis and CKD progression [37–40].

These findings have substantial implications, either for the single patient or for more generalized considerations. First of all, patients with a recognized genetic cause of paediatric onset of CKD might benefit from specific therapies or from the avoidance of ineffective and even potentially health threatening ones (e.g. immunosuppressive drugs in patients with genetic forms of SRNS) [41, 42]. In addition, molecular diagnostics enable prenatal testing in siblings of affected individuals and genetic counselling to the family, and may be of great help in assessing a patient prognosis. Finally, the categorization of disease entities by means of genetic testing is fundamental in assuring that the
and young children was $-2.33$ and $-1.65$, respectively, whereas it was only $-0.93$ for adolescents [27]. This is not unexpected, considering that one-third of total growth occurs in the first 2 years of life, so infants with CKD are at a great risk of severe growth retardation with a serious long-term impact on final height [21, 46, 47]. In children with CKD the risk factors that contribute to impaired growth include: malnutrition, metabolic acidosis, mineral and bone disorders, anaemia, and fluid and electrolyte abnormalities [48–51]. However, especially after infancy and early childhood, growth failure is mainly due to disturbances in growth hormone (GH) metabolism and its main mediator, insulin-like growth factor-I (IGF-I) [52, 53]. In fact, in infants and young children, growth is principally dependent on nutrition, which has a much greater impact on growth than the GH-IGF-I axis [52]. Therefore, inadequate nutrition (due to anorexia or vomiting) appears to be the most important factor contributing to growth impairment at that age and maximizing caloric intake to at least 80% of requirements has been found to effectively improve growth in children who developed CKD as infants [52, 53]. Treatment over 2 years with recombinant human growth hormone (rhGH) has been shown to be effective without any major adverse effects [45, 54–56]. A consensus paper on the use of rhGH in CKD recommends that all children with HTSDS <3rd percentile or with height velocity standard deviation score $<-2$ SD should be treated with rhGH after metabolic and nutritional abnormalities have been corrected [57]. Furthermore, the 2005 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease suggest avoiding rhGH therapy in children with poorly controlled mineral and bone disease [58]. In summary, even though rhGH therapy is unavoidable in most cases, an effective management of growth impairment in children with CKD must take into account all the nutritional and metabolic aspects of this disease.

**Chronic kidney disease–mineral and bone disorder**

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism due to CKD that is defined by the presence of one or a combination of the following findings: abnormalities in calcium, phosphorus, parathyroid hormone (PTH) or vitamin D metabolism; abnormalities in bone histology, linear growth, or strength; vascular or other soft tissue calcifications [59]. Renal osteodystrophy is an aspect of CKD-MBD that refers only to bone pathology. A prompt and effective management of mineral and bone disorders of CKD during childhood is of utmost importance. In fact, changes in calcium and phosphorus metabolism can significantly alter bone
remodelling and somatic growth. Optimization of bone health, growth and final adult height must be a focus of CKD management in children [59, 60]. Furthermore, paediatric nephrologists must be aware that an effective treatment of CKD-MBD affects the progression of cardiovascular disease, as phosphate is also a strong vascular toxin either in its own right or through its effect on PTH and fibroblast growth factor 23 [61, 62]. Despite international guidelines for the management of CKD-MBD [58], many patients still have a poorly controlled mineral metabolism, especially in the later stages of CKD. This is shown in a report of data collected by the International Pediatric Peritoneal Dialysis Network on 900 children worldwide, where PTH levels were over five times above the upper limit of normal values in ~50% of the patients. The highest levels were associated with higher phosphate and lower calcium levels. Phosphate control begins with dietary restriction. Thus, it is advisable for nephrologists to work closely with a specialized dietician from the very early stages of CKD. However, dietary restriction is very rarely adequate and phosphate binders become necessary even earlier than in adult patients [62–64], due especially to the unpleasant taste of this medication and the need for its ingestion at every meal. In general, the goal of therapy is to normalize mineral metabolism with the aim of improving growth and bone strength and, at the same time, reducing bone deformities and minimizing the progression of extra-skeletal calcification [65, 66].

Anaemia

Anaemia is a common complication in children with CKD causing many adverse clinical consequences, including poor quality of life, depressed neurocognitive ability, reduced exercise capacity and progression of cardiovascular risk factors, such as left ventricular hypertrophy (LVH) [67–70]. In adult patients with CKD, the diagnosis of anaemia is made and further evaluation warranted when haemoglobin concentration is <13.5 g/dL in men and <12 g/dL in women [71]. On the other hand, the diagnosis of anaemia in children with CKD is not as straightforward. The National Kidney Foundation KDOQI (NKF-KDOQI) clinical practice guidelines use reference data from National Health and Nutrition Examination Survey (NHANES) III to define normal values in the paediatric population and recommend initiating an evaluation for anaemia when haemoglobin levels fall below the age-specific and sex-specific 5th percentile value [71–73]. Anaemia increases in prevalence with advancing stages of CKD. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) show that the prevalence of anaemia in children is 73% at CKD stage III, 87% at stage IV and >93% at stage V [72, 74]. Anaemia of CKD is the result of many interacting factors, but decreased production of erythropoietin by the unhealthy kidney and iron dysregulation (including iron deficiency and iron-restricted erythropoiesis) are the primary defects [75–78]. Treatment with recombinant human erythropoietin (rHuEPO) is safe and effective, both in children with conservative-treated CKD and in those on maintenance dialysis [79, 80]. As in adults, the goal of this treatment is to achieve target haemoglobin levels of approximately 11 g/dL or slightly greater. Evidence shows that, both in adult and children, haemoglobin levels >13 g/dL are not associated with improved patient outcomes (including lower mortality, less frequent hospitalization, and less severe LVH) [71]. Interestingly enough, the dosing requirements of rHuEPO usually differ markedly between children and adults. Data from NAPRTCS show that, to achieve and maintain target haemoglobin levels, young children require higher rHuEPO doses than adults, ranging from 275 U/kg to 350 U/kg per week for infants, to 200–250 U/kg per week for older children [81, 82]. The underlying mechanism related to the need for such high rHuEPO doses has not yet been fully understood, but is probably due to a greater amount of non-haemopoietic erythropoietin binding sites (e.g. kidney, endothelium, brain, heart, skeletal muscle and retinal cells) in children, which decreases the bioavailability of the drug at its therapeutic sites [72, 83]. Supplemental iron therapy (either oral or intravenous) is also necessary for the treatment of anaemia in children with CKD. However, normal or above-normal ferritin levels in CKD, as in many other chronic diseases, could be a marker of inflammation and may not reflect the total iron body stores [84–86].

Hypertension

Unlike many of the complications of CKD, hypertension can be present from the earliest stages of the disease and its prevalence increases as GFR progressively declines [87, 88]. A recent work by the Chronic Kidney Disease in Children (CKID) study group showed that hypertension was present in 54% of participants at the time of enrolment and, even more strikingly, 48% of the children had high blood pressure (BP) levels despite the use of antihypertensive medications, which rarely included renin-angiotensin-aldosterone system inhibitors (RAAS-I). Interestingly enough, when BP was measured with a 24-h ambulatory BP monitoring (ABPM), children with CKD showed higher systolic and diastolic variability and lower heart rate variability compared with children without hypertension with CKD. These factors represent potential precursors for cardiovascular morbidity in adults [89]. Moreover, 38% of the CKID cohort had so-called masked hypertension (normal office BP but elevated ambulatory BP), which is another known risk factor for LVH [88, 89]. Studies performed in adults have clearly demonstrated that an effective control of BP reduces not only cardiovascular morbidity and mortality, but also the rate of progression of CKD [89–91]. Similarly, the renoprotective effect of RAAS-I, especially for proteinuric CKD patients, is now considered an unquestionable fact [91]. In the paediatric population, the ESCAPE trial of 385 children with CKD showed that patients randomly assigned to intensified BP control (BP <50th percentile) had a 35% relative risk reduction in reaching the primary endpoint of a decline of 50% in the GFR or ESRD compared with those in the conventional BP control group (BP 50th–90th percentile). All patients were treated with ramipril and, when needed, other antihypertensive medications that did not target the renin-angiotensin system were added in order to achieve targeted BP control [90, 92].

In summary, data from CKID and other studies show that underdiagnosis and inadequate control of BP occurs in children with CKD. To improve the recognition of hypertension in paediatric CKD patients, a 24-h ABPM monitoring should be performed whenever possible and the use of RAAS-I should be part of an effective antihypertensive medication management, especially in children with proteinuric disease.

Cardiovascular complications and death

It is well known that adults with CKD have significantly increased rates of cardiovascular morbidity and mortality compared with the general population [61, 93, 94]. However, increased cardiovascular risk is not unique to adults with CKD and several reports confirm that cardiovascular disease (CVD) is the leading cause of death also in the paediatric CKD population, with a risk 1000 times higher in the ESRD group compared with the age-matched non-CKD population [87, 95, 96]. The American Heart
Association’s guidelines for cardiovascular risk reduction in high-risk paediatric patients classified children with CKD in the highest risk group for the development of CVD, alongside individuals with homozygous familial hypercholesterolaemia, diabetes mellitus type 1, heart transplantation or coronary aneurisms due to Kawasaki disease [97].

Epidemiological and clinical studies have provided evidence that cardiovascular anomalies begin early in the course of renal failure, irrespective of the age of onset, and rapidly progress when dialysis is initiated [95, 98]. CVD in the CKD population ensues from a combination of traditional (e.g. hypertension, dyslipidaemia, abnormal glucose metabolism and obesity) and CKD-related risk factors (e.g. increased calcium-phosphorus product, hyperparathyroidism and anaemia) [87]. As CKD and dialysis are relatively uncommon in childhood, large multicentre and longitudinal studies are difficult to perform. Consequently, establishing and predicting the cardiovascular risk in this population is even more difficult [95, 99]. What is well known is that the cardiovascular causes of mortality are slightly different in children with CKD compared with adults with CKD. Adult cardiovascular deaths are mainly determined by coronary artery disease and congestive heart failure, while the leading causes of cardiac death in children with CKD are arrhythmias, valvular diseases, cardiomyopathy and cardiac arrest [61, 94]. The difference between the two populations may in part be attributed to the lower prevalence of classic risk factors for atherosclerosis in children with CKD.

From a pathophysiologic point of view, all the cardiovascular abnormalities that occur in adults with CKD are also present, to some extent, in children with CKD. As in adults, endothelial dysfunction appears early in the course of renal disease and has been observed in children with CKD undergoing conservative therapy as well as in children on dialysis [99, 100]. Arterial stiffening due to intimal calcification is commonly found in older patients with ESRD and is associated with classic risk factors for atherosclerosis, such as age, diabetes mellitus, smoking, high low-density lipoprotein cholesterol levels and inflammation [99]. On the other hand, diffuse and non-occlusive arterial stiffening found in children and young adults with ESRD is more often due to medial calcification and is strongly associated with uraemia-related specific factors, such as hypertension, long-term dialysis and high serum phosphate levels [99–101]. Furthermore, most studies show that LVH is the most common cardiac abnormality in children with CKD, and it develops even when CKD is mild and progresses as kidney function declines [87, 102]. This remodeling causes firstly a predominantly diastolic dysfunction and ultimately leads to systolic dysfunction and cardiac failure. LVH influences also the conductive properties of the myocardium and exacerbates the risk of dangerous arrhythmias [96, 103].

In conclusion, even though classic risk factors for atherosclerosis are less prevalent in children than in adults with CKD, markers of subclinical cardiovascular damage are present also in paediatric patients [99, 104]. Several modifiable risk factors, including hyperphosphataemia, hyperparathyroidism, anaemia and hypertension, independently predict the presence of cardiovascular abnormalities in these cases. An effective control of these non-traditional risk factors of CVD could improve the survival and the future global health of these patients.

**Concluding remarks**

CKD is a sly disease. Although relatively uncommon in children, CKD can be a devastating illness with many long-term consequences (Figure 3). In fact, the mortality rate for children with ESRD receiving dialysis therapy is 30–150 times higher than in the general paediatric population and the life expectancy for a

![Fig. 3. Clinical complications of CKD: a double perspective. The picture shows the correspondence between clinical features and complications of CKD with onset during childhood (left, top) and the relative consequences in adult life (right, top). On the other hand, clinical and laboratory findings of kidney disease in an adult (right, bottom) may find an explanation in kidney functional and/or structural abnormalities that already existed during infancy and childhood (left, bottom) but that may have been missed or underdiagnosed because of being clinically silent. Therefore, nephrologists, should have a global vision of their patients, regardless of whether the patient with CKD is a child or an adult: the first with a look towards the future, the other to the past. To underline this aspect, each box on the left side of the picture corresponds to one on the right side, as highlighted by the colour code. CKD, chronic kidney disease; GH-IGF-I, growth hormone and insulin-like growth factor I; LVH, left ventricular hypertension; CKD-MBD, chronic kidney disease-mineral and bone disorder; CV, cardiovascular; FSGS, focal segmental glomerulosclerosis.](image-url)
child on dialysis is ~50 years less than a healthy child [9, 19, 105]. Kidney transplantation is characterized by a significant improvement in prognosis and is the best therapeutic option for children with ESRD. However, most of the complications of this clinical syndrome have consequences on the patients’ health well before kidney function is irreversibly lost, even when it is maintained stable over time with conservative therapy.

In addition, despite similarities to the adult disease, CKD in children presents unique features and challenges that are not usually faced by adult patients and that make paediatric CKD a stand-alone nosologic entity. Nevertheless, paediatric nephrologists should be aware that complications in childhood CKD will have consequences well beyond paediatric age and influence outcomes of affected young adults with CKD (Figure 3). On the other hand, nephrologists who take care of young adults with CKD or adults with childhood CKD should understand the unique characteristics that CKD presents in children, especially the aetiology, in order to significantly ameliorate their patients’ care (Figure 3).

In summary, nephrologists, whether caring for children or for adults with CKD, should have a global vision of their patients: the first with a look towards the future, the other to the past.

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Conflict of interest statement

The results presented in this review have not been published previously in whole or part. All the authors declare no conflict of interests.

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