Kidneys - kindergarten to graduation

From diapers to the graduation hat, kidneys have to mature from their infancy, childhood, and adolescence before reaching adulthood. This crucial journey of kiddy kidneys needs a favorable environment for growth, development and nourishment so as to graduate into young adult kidneys at 18 years of age. Caring for such a dynamic phase of kidney maturation becomes the prime responsibility of the pediatric nephrologist. On account of the World Kidney Day 2016, that focuses on Kidney disease and children, it is befitting to look at the unique challenges posed by these pediatric kidneys from an Indian perspective.

The Very Beginning

The critical number

Nephrogenesis begins at 9th week of gestation and continues through 34th–36th weeks of gestation after which time no new nephrons are formed. With an average of 1 million nephrons per kidney,[1] it is predicted that there is an increase of 257,426 glomeruli per kilogram increase in birth weight.[2] Clinical surrogates for low nephron number and susceptibility to hypertension and renal disease in adulthood are low birth weight, preterm birth, short stature, low kidney volume, glomerulomegaly, gene polymorphisms, and maternal gestational hyperglycemia.[3] Exploring the concept of adult diseases having their roots in childhood, South Asian adults are at high risk for premature severe chronic kidney disease (CKD)[4,5] and harbor a greater propensity to third-trimester growth restriction which impacts on the developing kidney, leading to reduced kidney volume.[6] Besides the fact that India is the cradle for 40% of all low birth weight babies in the developing world,[7] maternal nutrition including Vitamin A status could influence nephrogenesis and renal volumes in the newborn.[8]

Developmental pangs

Congenital anomalies of the kidney and urinary tract (CAKUT) are part of a syndrome or sequence that leads to end-stage renal disease in children. The genetic diagnosis of CAKUT has proven to be challenging due to genetic and phenotypic heterogeneity and influence of epigenetic and environmental factors on kidney development.[9,10] Specific renal diseases such as polycystic kidney disease and primary hyperoxaluria, known to be prevalent in India, progressing to CKD, share an autosomal recessive inheritance. Consanguineous marriage is a cultural phenomenon that is associated with kidney disease and is prevalent in many Asian countries[11] including rural India. Consanguinity and genetic predisposition add to the risk of CAKUT, reflux nephropathy, and urinary tract obstruction that are major contributors to CKD.

Just born kidneys

Newborn kidneys are immature and susceptible to hypoperfusion, low glomerular filtration rate, high renal vascular resistance, high plasma renin activity, decreased intercortical perfusion, and decreased reabsorption of sodium in the proximal tubules.[12]

The paucity of Indian data on neonatal acute kidney injury (AKI) is alarming. Besides sepsis and hypovolemia, Gupta *et al*.[13] highlighted perinatal asphyxia as an important risk factor for neonatal AKI. With limitations in obtaining baseline serum creatinine values and urine output assessment in neonates, many categorical definitions of neonatal AKI such as the Neonatal Risk, Injury, Failure, Loss of kidney function and End stage kidney Disease (nRIFLE), AKI network (AKIN), and modified kidney disease improving global outcomes criteria (KDIGO) pose challenges in the stratification of levels of severity and early recognition of AKI in clinical practice.[14]

The Formative Years

An interesting feature of pediatric renal diseases is that there is a difference in the occurrence of disease with age and variation in the manifestation of the same disease at different phases of childhood: While tubular disorders predominate during infancy and early childhood, majority of glomerular diseases are generally seen beyond the first few years of life. Hypertension, urinary tract infection, and CKD are notorious to have contrasting clinical manifestations that vary with age.

Challenging signs

As in adults, hematuria, oliguria, and edema are the most striking signs of renal disease, commonly a signature of glomerular disease. However, in children, many signs of kidney disease are either hidden or they mimic other

systemic diseases. For example, failure to thrive or growth retardation, recurrent vomiting, and respiratory distress could be the only signs of CKD or a tubular disorder. Bone deformities and neurological manifestations could be indicators of underlying tubular disorders.

The Pandora's box on genetics

Molecular genetics and genomic science have opened new challenges in patient care. In India, Pediatric nephrology has made considerable progress in establishing genetic analysis for diseases such as nephrotic syndrome and hemolytic uremic syndrome.

The acute kidney injury-chronic kidney disease continuum

The incidence of pediatric AKI (Acute Kidney Injury) in hospitalized children[15] is as high as 36%. The etiological spectrum ranges from tropical systemic infections, sepsis with multi-organ dysfunction, and snake envenomation to primary renal diseases. Use of alternative forms medicine poses an additional challenge. Neonates, who survive sepsis or asphyxia with neonatal AKI,[16] including urinary tract obstruction, are at high risk for developing CKD. Systematic monitoring of the AKI-CKD clinical syndrome is the need of the hour. Sensitization and active assessment of possible sequelae of AKI that has been proposed by the ASSESS-AKI study[17] need implementation in neonates and children in our country.

Renal recovery

To ascertain renal recovery in children is a challenge.[18] Glomerular filtration rate (GFR) increases over the 1st year of life from 15 to 90 ml/min/1.73 m^2 resulting in difficulty in deriving an AKI threshold.[19] The current CKD studies and definitions exclude children under 1 year of age making the diagnosis of CKD difficult in small children.[20] Finally, children are born with substantial relative renal reserve, with more than sufficient clearance capacity in relation to their metabolic output. As estimated renal function is associated with height in children, linear growth plays a role in preserving renal function.

The chronic blues

Chronic glomerulonephritis, hypodysplasia, and obstructive uropathies have dominated the list of causes of pediatric CKD in many developing countries.[21] Advances in the management strategies and availability of certain immunosuppressive therapies have helped control common glomerular diseases.[22,23] Though dialysis therapy is considered a bridge to transplantation in children, we are faced with many challenges related to cardiovascular morbidity, nutrition, anemia, and bone mineral disease in addition to the issues of financial burden and quality of life.

The gift of life

Live related and deceased organ renal transplantation in children is gathering momentum in a few centers across the nation.[24-28] However, the real challenge lies not only in escalating the number of transplants but more importantly in optimizing the long-term care of the allograft posttransplant. The overall 5 years and 10 years graft survival are reported to be between 80–86% and 70–75%, respectively.[24-28] Urological issues and interventions play a vital role in pediatric transplantation. Focal segmental glomerulosclerosis is a major cause for End Stage Renal Disease, and we have shown the variation in the genetic polymorphisms among Indian children[29] with recurrence post renal transplant[30] being an additional economic burden.

Graduation

The graduation day for kidneys is when the adult nephrologist takes over care of young adult kidneys. The weaning period from the pediatric nephrologist has to be a gradual process undertaken in Transition Clinics. Care of kidneys in children often demands a multidisciplinary approach with formal psychosocial counseling services, which may need focus into adulthood.

Parenting kidneys is just not treating children with kidney disease. The broader perspective lies in implementing Preventive strategies; Outreach initiatives for prompt and early diagnosis; Training and collaborations for faculty development and capacity building; and relevant research programs for holistic renal care - *A message that should reverberate not only on World Kidney Day but on every other day!*

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Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.177731

How to cite this article: Iyengar AA. Kidneys - kindergarten to graduation. Indian J Nephrol 2016;26:77-9.