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Overview of Polycystic Kidney Disease in Children

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Renal cysts are not rare and may appear in the fetus or in latter life. Some of these cysts are isolated and benign while others may be the harbinger of significant renal injury. Cysts can compress neighboring tissue causing a reduction in renal function. Compression of blood vessels can lead to hyperreninemic hypertension. Depending on the type and number of cysts and the disorder that caused the cystic lesion, the renal injury can manifest clinically in late childhood or adulthood or at the time of birth. Some cystic kidney disease is so severe that the infant is born with little or no renal function. In some disorders there are associated abnormalities of other organs. This issue of Current Opinion in Pediatrics is devoted to renal cystic disease and its related manifestations.

Renal cysts are often present in dysplastic kidneys where the normal formation of the kidney has gone terribly wrong and the architecture of the kidney is replaced by glomerular and tubular remnants, fibrosis, metaplastic tissue such as cartilage and often cysts [1]. Dysplastic kidneys either have little or no function and can be associated with other congenital anomalies. The type of dysplasia with multiple large cysts is called multicystic dysplastic kidney and it can be unilateral or bilateral. The cysts do not connect and there is no renal pelvis present on prenatal sonograms. In multicystic dysplastic kidneys, the ureter is usually not patent which is likely a pathologic factor leading to multicystic dysplasia. In other forms of dysplasia there can be genetic factors, toxins or other stochastic factors that lead to abnormal kidney development with or without cysts. Multicystic dysplastic kidneys have no function and the outlook for the newborn with a multicystic dysplastic kidney is dependent on the function of the contralateral kidney. If the contralateral kidney and collecting system are normal, there is an increased likelihood of mild proteinuria and hypertension, but the prognosis is excellent if there are no associated congenital anomalies. If the contralateral kidney is normal there should be compensatory hypertrophy. However, there is a 40% likelihood of a contralateral renal abnormality that may predispose to urinary tract infections or may be more severe causing chronic kidney disease. If there is severe bilateral dysplasia and no urine output there will be a paucity of amniotic fluid leading to pulmonary hypoplasia. The infant will not be buffered by the amniotic fluid and will thus have a compressed face, clubbed feet which along with pulmonary hypoplasia is called Potter's Syndrome. Neonates with Potter's syndrome often do not survive the neonatal period.

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Conflicts of interest: None

There are dozens of inherited causes for renal cystic kidney disease. Some of these cystic kidney diseases manifest in utero, while others are clinically silent throughout life. Some cysts are microscopic while others are several centimeters in diameter. Despite the multiple causes, associated abnormalities, and clinical manifestations, inherited renal cysts appear to have a commonality; all inherited cystic kidney diseases are due to mutations in the cilia or basal body/centrosome complex. Cilia are present on most epithelial cells and function as either a sensory organelle as in the kidney or as a motor organelle that aids in movement of secretions as in our respiratory tract. In the kidney, cilia are on apical surface of tubular cells anchored to the cell at the basal body/centrosome complex. While tubular ciliary function is not well understood, cilia sense urinary flow. When cilia are bent by tubular flow, there is an increase in intracellular calcium. How a mutation in one of the ciliary proteins leads to renal cysts and various other abnormalities is the focus of research in many laboratories. Dr. Katherine Dell discusses the role of cilia in PKD in her review in this issue of Current Opinion in Pediatrics.

When one thinks of polycystic kidney disease, one often thinks that there are two types. Autosomal recessive polycystic kidney disease is the one that presents in neonates sometimes infants and autosomal dominant polycystic kidney disease is a disease of adults. Autosomal recessive polycystic kidney (ARPKD) disease is characterized by secular dilatation of one segment of the kidney tubule, the cortical collecting duct. ARPKD is due to a mutation in a gene called PKHD1 (polycystic kidney and hepatic disease-1), which encodes a huge protein called polyductin or fibrocystin which localizes to cilia. The “cysts” are not truly cysts but dilated tubules. The kidney thus does not usually have cysts that one can recognize as a cyst on ultrasound but usually are manifest by large echogenic kidneys on prenatal or postnatal sonograms. There is a wide spectrum of disease in which may have very severe renal disease presenting with Potter’s syndrome to less severe renal injury and more severe extrarenal manifestations. Patients will often have flank masses due to nephromegally on neonatal exam and often have very severe hypertension. The most frequent extrarenal manifestation of ARPKD is in the liver leading to congenital hepatic fibrosis. In ARPKD the hepatocyte is spared but there is extensive periportal fibrosis which can lead to portal hypertension and its complications. Professor Peter Hoyer elegantly describes the renal and extrarenal manifestations of ARPKD and the variable prognosis of this disorder.

Autosomal dominant polycystic kidney (ADPKD) disease is due to a mutation of one of two genes designated PKD1 and PKD2. As noted PKD can manifest at any age with variable severity but on an average, ESRD occurs in PKD1 in the fifth decade of life and PKD2 in the seventh decade of life. PKD1 is due to a mutation in polycystin 1 which is a huge membrane bound protein of unknown function, while PKD2 encodes a calcium channel that binds to PKD1. Unlike ARPKD, cysts can occur anywhere along the nephron. ADPKD is the fourth most common cause for end stage renal disease in the United States. However, only about 50% of patients with ADPKD develop end stage renal disease in their lifetime. ADPKD is a systemic disease and it can affect other organs leading to mitral valve prolapse, cerebral aneurisms, liver cysts, pancreatic cysts, and hypertension. A family history may be positive but spontaneous mutations occur in about 10% of patients with ADPKD. ADPKD

can be silent or have severe manifestations in children. ADPKD in children is discussed in the article by Melissa Cadnapaphornchai.

Nephronophthisis is an autosomal recessive disease that is not well known by most pediatricians, but it is the cause for 5-10% of childhood end stage renal disease in the United States. The cysts with nephronophthisis are usually small and may not be detectable on a renal sonogram. Patients often present with a renal salt wasting and a concentrating defect leading to polydipsia and polyuria. As renal function deteriorates, hypertension and anemia are major clinical manifestations. Nephronophthisis is actually a family of diseases and approximately 20 different mutations causing the disorder have been identified. Patients with nephronophthisis can have extra renal manifestations including blindness, cerebellar disorders, bone abnormalities and developmental delay. The renal and extrarenal manifestations of this family of disorders are discussed by Matthias Wolf.

MicroRNAs are 20-22 nucleotide noncoding RNA's that regulate RNA expression. These recently discovered regulatory factors are a family of short RNA fragments that can bind to RNA resulting RNA degradation and a decrease in RNA translation. MicroRNAs regulate a myriad of functions of every organ including the kidney, where they play a role in renal development, salt and water transport and the renin angiotensin system [2]. MicroRNAs likely also have a role in kidney disease including polycystic kidney disease. The article by Drs. Phua and Ho introduce the reader to the field of microRNAs and how they are synthesized and affect mRNA translation. The role of microRNAs in the pathogenesis of polycystic kidney disease is now beginning to unfold and is discussed in this review.

In the final review, Dr. John Bissler discusses therapeutic interventions aimed at decreasing the rate of cyst growth. He discusses studies aimed at both decreasing the rate of cellular proliferation and fluid secretion. This review offers practical advice for patients that care for children with polycystic kidney disease.

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