NEPHRONOPHTHISIS

A large and growing number of genetically distinct but related autosomal recessive disorders are referred to as nephronophthises. These should not be confused with the adult-onset autosomal dominant medullary cystic kidney diseases discussed above, despite the often confusing nomenclature seen in older medical literature. Nephronophthisis is quite rare but is nevertheless the most common inherited childhood form of kidney failure requiring kidney replacement therapy.

Like ADPKD and ARPKD, the various genetically heterogeneous entities that fall under the category of nephronophthisis (NPHP) are disorders of ciliary function. Mutations in a very large number of genes have been identified that lead to NPHP under an autosomal recessive pattern of inheritance. The various forms of NPHP share common features, including tubulointerstitial fibrosis, corticomedullary cysts, and progressive CKD, leading to renal failure. Proteinuria is absent or mild, and the urine sediment is not active.

NPHP is often divided into infantile, juvenile, and adolescent forms. The juvenile form is the most frequent and usually caused by mutations in the *NPHP2* gene. The infantile form, usually caused by *NPHP2* mutations, is associated with end-stage kidney failure in early childhood. Patients with the adolescent form of NPHP typically develop end-stage kidney failure in early adulthood. The products of the NPHP genes are referred to as nephrocystins. *NPHP1* through *NPHP16* have been reported; some are referred to by other names as well.

NPHP can present as an isolated finding or be part of several multiorgan syndromes. Neurologic abnormalities are present in a significant number of patients. Bone and liver abnormities are seen in some NPHP patients. Senior-Løken syndrome is defined by the presence of NPHP with retinitis pigmentosa. Joubert's syndrome is defined by multiple neurologic findings, including hypoplasia of the cerebellar vermis. Some forms of this genetically heterogeneous syndrome include NPHP as a component.

The multisystem disease Bardet-Biedl syndrome (BBS) is defined clinically by a spectrum of features, including truncal obesity, cognitive impairment, retinal dystrophy, polydactyly, developmental urogenital abnormalities, and kidney cysts. The kidney phenotype is NPHP-like, with small cysts deriving from the tubules, tubulointerstitial and often secondary glomerular disease, and urine concentrating defects. There are 18 BBS genes cloned. BBS follows autosomal recessive inheritance. Like ADPKD, ARPKD, and NPHP, BBS is a disease of abnormal ciliary function.

The multiple genes and gene products (nephrocystins) that are responsible for NPHP are expressed in cilia, basal bodies, and the centrosomes of kidney tubule cells. It has been hypothesized that all of the NPHP gene defects lead to a clinical phenotype by interfering with the regulation of PCP.

There are no specific clinical tests that define NPHP. Genetic diagnosis is possible but cumbersome because of the large number of genes that can be responsible. There are no specific therapies for NPHP. Rather, therapy is aimed at treating signs of these diseases as well as the systemic abnormalities seen with all CKDs. Chronic dialysis or kidney transplantation is eventually required for NPHP-affected individuals.

KARYOMEGALIC TUBULOINTERSTITIAL NEPHRITIS

Karyomegalic tubulointerstitial nephritis is an exceptionally rare form of kidney disease with adult-onset progressive kidney failure. Kidney biopsy shows chronic tubulointerstitial nephritis, as well as interstitial fibrosis. This is a recessive disorder caused by inheritance of two mutant copies of the *FAN1* gene. *FAN1* encodes a component of a DNA repair machinery complex. Individuals with two mutant *FAN1* genes are genetically sensitized to the effect of DNA damage. Kidney histology shows karyomegaly in addition to the nonspecific findings of interstitial fibrosis and tubular atrophy.

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney (MSK) is often grouped together with inherited disorders of the kidney affecting tubule growth and development, although it is usually a sporadic finding rather than an inherited phenotype. MSK is caused by developmental malformation and cystic dilatation of the renal collecting ducts. The medullary cysts seen in this entity can be quite variable in size.

MSK is usually a benign entity. The diagnosis of MSK is often made incidentally. In the past, the diagnosis of MSK was often made by intravenous pyelography (IVP). CT scans, which have replaced IVPs for much routine kidney imaging, are not as sensitive in detecting MSK.

MSK is associated with an increased frequency of calcium phosphate and calcium oxalate kidney stones. Altered flow characteristics in the kidney tubules may lead to the development of formation of a nidus for stone formation. Kidney stones in this group are treated the same as are kidney stones in the general population. MSK patients also often exhibit reduced kidney concentrating ability and an increased frequency of urinary tract infections.

CONGENITAL ABNORMALITIES OF THE KIDNEY AND URINARY TRACT

The structural abnormalities known as the congenital abnormalities of the kidney and urinary tract (CAKUTs) are a group of etiologically and phenotypically heterogeneous disorders. Some form of CAKUT is estimated to occur in up to 1 in 500 live births. Specific abnormalities classified as part of the CAKUT spectrum include kidney hypoplasia, kidney agenesis, ureteropelvic junction obstruction, and vesicoureteral reflux.

CAKUT can be the cause of clinically significant problems in both adults and children. However, it is a major contributor to kidney failure in children, accounting for more than one-third of end-stage kidney disease in this group.

CAKUT is typically a sporadic finding but can also cluster in families. Familial forms can be observed as parts of multisystem developmental syndromes. A growing list of specific genes have been identified, which when mutated lead to syndromic forms of CAKUT. For example, the branchio-oto-renal syndrome, characterized by developmental abnormalities in the neck, ears, and kidney, can be caused by mutations in the *EYA1* and *SIX1* genes. Mutations in the *PAX2* transcription factor gene can cause the autosomal dominant renal coloboma syndrome, characterized by optic nerve malformations and hypoplastic kidneys.

In many instances, CAKUT is caused by environmental influences rather than genetic alterations. For example, renal tubular dysgenesis, defined by altered tubule development, can be caused by prenatal exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

MITOCHONDRIAL DISEASE

Inherited disorders of the mitochondrial genome (discussed elsewhere in this text [Chap. 85e]) commonly affect kidney function. Thirteen of the genes involved in encoding components of the mitochondrial respiratory chain are located on the mitochondrial genome that is inherited maternally. The remainder of these components is encoded by the nuclear genome. These defects of oxidative phosphorylation may affect multiple organs and tissues.

Neuromuscular disease is the best recognized part of this complex phenotype. Kidney disease is now recognized as a common component as well. Tubulointerstitial disease may be seen on kidney biopsy, and progression to kidney failure may occur. Glomerular involvement, manifest as proteinuria and glomerulosclerosis, can also develop. Changes in proximal tubule activity are the most common renal phenotype. Patients may have several defects in proximal tubule transport, including the Fanconi syndrome. Some patients may also have acidosis, hypophosphatemic rickets, hypercalciuria, glycosuria, and tubular proteinuria. Decreased urine concentrating ability is common.

GLOBAL CONSIDERATIONS

The disorders discussed above are all seen worldwide. In addition, a previously unrecognized epidemic of kidney disease is leading to very high rates of kidney failure in and near the