Inherited Kidney Diseases in Dogs and Cats

George E. Lees
Texas A&M University, College Station, Texas

OVERVIEW OF THE ISSUE

Inherited kidney diseases have been recognized in several breeds or kindreds of dogs and cats, and more examples of such conditions are likely to be identified as renal diseases that occur in a familial pattern are investigated thoroughly. In affected breeds/kindreds, accurate diagnosis of familial nephropathies is especially important because of the potential health and selective breeding implications for related animals. Additionally, because juvenile onset of chronic renal failure is the most common consequence of familial renal disease, discovery of kidney disease in a young dog or cat often evokes concern about whether the condition is congenital or acquired, and if it is congenital, whether or not it is inherited.

More familial renal diseases have been described in dogs than in cats, but polycystic kidney disease in cats likely is the single most common inherited nephropathy that occurs in these companion animal species worldwide. The main categories of familial nephropathies are listed in **Table 1**. To date, the pathogenesis and causative gene defect have been determined for only a few inherited kidney diseases in dogs and cats. However, the pace of progress in this field is accelerating rapidly because of advancing technology and increasing availability of genetic information regarding these species.

Most familial renal diseases are progressive and ultimately fatal, although the rate of progression often varies considerably among individuals with the same disorder. Therapeutic efforts generally are focused on combating complications (e.g., hypertension, urinary tract infection) as they arise and using conventional strategies for medical management of chronic renal failure to minimize disease progression and uremia.

CLINICAL FINDINGS

The clinical syndrome produced by most familial nephropathies is chronic renal failure, which often develops while the animals are adolescents or young adults. In dogs with renal dysplasia and some primary glomerulopathies, onset of renal failure usually occurs at 3 months to 3 years of age, with peak occurrence at about 1 year of age. However, many familial kidney diseases often produce renal failure somewhat later in life. For polycystic kidney disease, some primary glomerulopathies, amyloidosis, and glomerulonephritis, onset of renal failure often is at 3-7 years of age, depending on the condition.

Reduced appetite or anorexia, stunted growth or weight loss, polyuria and polydipsia, and vomiting are the most common clinical signs in dogs and cats with renal failure due to a familial nephropathy. Other signs that are often reported include poor hair coat, halitosis, and diarrhea.

Physical examination findings often include thin body condition, dehydration, mucous membrane pallor, uremic breath odor, and oral ulceration. Fibrous osteodystrophy or rubber jaw is occasionally observed, mainly in dogs that develop renal failure before 6 months of age. The kidneys of animals, especially cats, with polycystic kidney disease often are palpably enlarged. Otherwise, the kidneys usually are normal or reduced in size. Dogs with severe renal dysplasia often have especially small kidneys.

Laboratory testing most often reveals the expected abnormalities associated with chronic renal failure, especially impaired urine concentrating ability, azotemia, hyperphosphatemia and nonregenerative anemia. These findings usually reflect the severity of the animal's renal failure independent of its cause. Urinalysis findings, however, frequently help discriminate among the common causes of juvenile or familial

nephropathy. Dogs with primary glomerulopathies and familial glomerulonephritis consistently have persistent renal proteinuria that emerges early in the course of disease and typically is of high magnitude (UPC $\geq$ 2). Dogs with renal dysplasia and dogs and cats with polycystic kidney disease usually exhibit little or no proteinuria, while proteinuria is an inconsistent finding that depends on the extent of glomerular involvement in dogs and cats with familial amyloidosis. Renal glucosuria is a consistent feature of the Fanconi syndrome in Basenji dogs but occasionally is observed in dogs with renal dysplasia or primary glomerulopathies. Bacterial urinary tract infection also sometimes develops as a secondary complication in dogs and cats with juvenile or familial nephropathies.

Diagnostic renal imaging is most helpful for animals with polycystic kidney disease in which a definitive diagnosis can be made by finding multiple cysts distributed in both kidneys using ultrasonography. In dogs with renal dysplasia, ultrasound can demonstrate abnormal size, shape, and sonic architecture of the kidneys, but it cannot distinguish renal dysplasia from other possible causes of small, fibrotic end-stage kidneys in affected dogs.

DIAGNOSIS

For specific kidney diseases that are known or suspected to be inherited in particular breeds, diagnosis of the condition generally rests on recognition of the expected clinical features, exclusion of other conditions that might produce similar signs, and ultimately upon identification of characteristic renal lesions.

The exclusion of other disorders (especially those that are potentially treatable) is a key step because a variety of acquired diseases may occur in the same breeds and age-groups of animals that might have familial nephropathies. Careful interpretation of the results obtained from a thorough clinical investigation (history, physical exam, blood pressure determination, complete urinalysis, urine culture, and appropriate diagnostic imaging) often is adequate for presumptive diagnosis of a familial nephropathy. Even when the diagnosis remains uncertain, however, such an investigation generally is sufficient to properly guide the animal's medical care. Nonetheless, definitive diagnosis of many familial nephropathies ultimately rests upon identification of characteristic lesions in kidney specimens obtained at necropsy or by biopsy.

Light microscopic examinations are sufficient for many disorders, but especially for glomerular diseases, transmission electron microscopic and immunopathologic studies often are needed as well. Prior planning generally is needed to assure that specimens that will be suitable for these specialized evaluations are obtained when the tissue is collected because special materials and procedures are required. Centers that perform such studies should be contacted for guidance.

In breeds or families known to be at risk for certain familial nephropathies, apparently healthy animals can screened with tests that will aid early identification of affected individuals. The foremost examples of such screening are the use of ultrasonography to identify polycystic kidney disease and urinalyses to detect persistent renal proteinuria in animals that are at risk for glomerular disorders.

When a juvenile nephropathy is identified, questions about inheritance of the condition frequently arise. For breeds in which the specific nephropathy that has been diagnosed is known to be inherited, genetic counseling can be provided. In most other circumstances, heritability of the condition remains unknown unless or until studies of related animals show a familial pattern of disease occurrence.

SELECTED SPECIFIC DISORDERS

Renal dysplasia

Renal dysplasia is defined as disorganized development of renal parenchyma that is due to abnormal differentiation. For definitive diagnosis of this category of conditions, microscopic observation of structures in the kidney that are inappropriate for the stage of development of the animal is required. The presence of immature glomeruli and tubules usually within radial bands adjacent to more normally developed tissue (*i.e.*, asynchronous differentiation of nephrons) is the most consistent feature. Other findings indicative of renal dysplasia include persistent immature mesenchyme, persistent metanephric ducts, atypical tubular epithelial proliferation, and (albeit rare in dogs) dysontogenic metaplasia. Secondary changes that are commonly observed include compensatory hypertrophy and hyperplasia of glomerular tufts and tubules, interstitial fibrosis, tubulointerstititial nephritis, pyelonephritis, dystrophic mineralization, cystic glomerular atrophy, microcystic tubules, retention cysts, and glomerular lipidosis.

Renal dysplasia is most extensively reported and presumed to be familial in Lhasa Apso and Shih Tzu dogs. Other breeds in which published reports have suggested that renal dysplasia occurs in a familial pattern are listed in Table 1. Additionally, juvenile nephropathies with microscopic features of renal dysplasia have been reported in one or more unrelated dogs of so many different breeds that it seems likely that the disorder occurs at least sporadically in all breeds. The causes and pathogenesis of canine renal dysplasia are unknown. Renal dysplasia is widely accepted to be the same disease entity in both Lhasa Apso and Shih Tzu dogs, but the whether the other familial or sporadic forms of renal dysplasia are fundamentally the same disease or different diseases having similar adverse effects on development of the kidneys in affected dogs is uncertain. To date, data documenting the validity of genetic testing for renal dysplasia have not been published for any breed.

Primary glomerulopathies

A number of primary glomerulopathies, including several of the most well characterized inherited renal diseases of dogs, have been described. Conditions in which an abnormality of the type IV collagen in the glomerular basement membrane (GBM) is known or suspected to cause the disease lead this category. All basement membranes contain collagen IV, but in the GBM, a special collagen network containing the α3, α4, and α5 chains of type IV collagen is crucial for long-term maintenance of normal structure and function of the glomerular capillary wall. When this α3-α4-α5(IV) network is not formed properly, the GBM deteriorates and initiates a process of progressive renal injury that leads to chronic renal failure. These conditions are analogous to the kidney disease that occurs in human Alport syndrome, which is a genetically and clinically heterogenous group of diseases. In dogs as in people, the mode of inheritance can be X-linked, autosomal recessive, or autosomal dominant.

X-linked hereditary nephropathies caused by mutations in the gene (COL4A5) encoding the α5(IV) collagen chain have been described in two canine families. The mutations that cause these diseases have been identified, but each is unique within its kindred. An autosomal recessive hereditary glomerulopathy also occurs in Cocker Spaniels (known in North America as English Cocker Spaniels) worldwide. These dogs presumably have a COL4A3 or COL4A4 mutation, but the causative mutation has not yet been identified. These disorders are characterized by abnormal composition of the type IV collagen in renal basement membranes, which can be demonstrated by special immunostaining techniques, and by distinctive ultrastructural GBM changes, which can be detected only using transmission electron microscopy.

Onset of persistent proteinuria is the first clinical sign and usually occurs at 4-8 months of age. Thereafter, renal function progressively deteriorates, usually causing azotemia by 6-12 months of age and death from renal failure at 9-18 months of age. The light microscopic features of the nephropathy are nonspecific, having the morphologic features of a membranoproliferative glomerulonephropathy accompanied by secondary tubulointerstitial changes.

Autosomal dominant inherited glomerulopathies have been described in Bull Terriers and Dalmatians, mainly from Australia. The disorders also are characterized by ultrastructural GBM abnormalities that can be identified only with transmission electron microscopy; the changes are similar to those of the X-linked and autosomal recessive conditions described above. In contrast, however, immunostaining of kidney from affected Bull Terriers and Dalmatians shows a normal pattern of type IV collagen α-chain expression in their basement membranes. The gene mutations that cause these nephropathies in Bull Terriers and Dalmatians have not been identified. Clinical expression of autosomal dominant glomerulopathies is variable. Affected dogs have proteinuria (UPC $\geq$ 0.3), but the onset of renal failure occurs at 11 months to 8 years of age in Bull Terriers and at 8 months to 7 years of age in Dalmatians.

Polycystic kidney disease

Autosomal dominant polycystic kidney disease is prevalent in Persian and Persian-cross cats, affecting approximately 38% of Persian cats worldwide. Recently, a single mutation in the feline *PKD1* gene has been incriminated as the cause of this disorder in many if not all affected cats. A stop mutation caused by a single nucleotide transversion in exon 29 (of 46) was found in the heterozygous state in each of 48 affected cats (41 Persians and one cat in each of seven other breeds) from the United States. Because the mutation is likely to be identical by descent within the breed, a DNA test is now possible to identify Persian and Persian-cross cats that have or will develop polycystic kidney disease, although the expectation that this single mutation causes the disease worldwide remains to be verified by further studies. In affected cats, multiple cysts form in both kidneys and occasionally in the liver. Renal cysts arise from tubules and occur in both the cortex and medulla. They form early in life and gradually become more numerous and larger in size as the cat ages. Detection of multiple cysts distributed in both kidneys using ultrasonography is diagnostic. Cysts sometimes can be detected in kittens as young as 6-8 weeks of age; however, because the number and size of cysts increase with time, sensitivity of ultrasound as a diagnostic test for polycystic kidney disease increased from 75% at 16 weeks of age to 91% at 36 weeks of age in one study. Cyst growth eventually causes renomegaly, which can be an incidental finding during physical examination of seemingly healthy cats, and renal failure ensues later in adult life (at 3-10, average 7, years of age).

Autosomal dominant polycystic kidney disease also has been described in Bull Terriers, mainly in Australia. Affected dogs are identified by ultrasonography when multiple ($\geq$ 3) cysts distributed in both kidneys are detected in dogs with a family history of the disease. The gene mutation that causes this disease has not been identified, but dogs at risk for the disease can be screened with ultrasonography prior to breeding to minimize production of additional affected animals.

Amyloidosis

In Shar Pei dogs, familial amyloidosis usually causes renal failure in dogs that are 1 to 6 (average, 4) years of age. Some dogs have a history of previous episodes of high fever and joint swelling, and this disease in Shar Pei dogs may be analogous to familial Mediterranean fever in humans. Some evidence suggests that amyloidosis in Shar Pei dogs is inherited in an autosomal recessive fashion. Affected Shar Peis invariably have moderate to severe medullary interstitial amyloid deposits, but only two-thirds have glomerular deposits. Proteinuria and other elements of the nephrotic syndrome, which reflect the severity of glomerular involvement, occur in some dogs. Amyloid frequently is also deposited in many other organs. Severe amyloid deposition in the liver may cause hepatomegaly, jaundice, or hepatic rupture.

In Abyssinian cats, familial amyloidosis probably is inherited as an autosomal dominant trait with variable penetrance. Renal amyloid deposits first appear between 9 and 24 months of age mainly in the medullary interstitium. Glomerular deposits usually are mild

but occasionally are severe, so proteinuria is a variable feature of renal amyloidosis in cats. Affected cats usually develop chronic renal failure at 1 to 5 (average, 3) years of age, but cats with mild deposits can live to be much older. Additionally, cats with severe medullary involvement sometimes develop papillary necrosis. Amyloid deposits often are also found in other organs, but in Abyssinian cats, extra-renal amyloid deposition usually is of little clinical consequence. In Siamese and Oriental cats with familial amyloidosis, however, severe amyloid deposition occurs predominantly in the liver and mainly causes intra-abdominal hemorrhage from hepatic rupture. Nonetheless, amyloid deposition also occurs in the kidneys and leads to renal failure in some affected cats.

Immune-mediated glomerulonephritis

A familial disorder that causes protein-losing enteropathy, protein-losing nephropathy, or both has been described in Soft-Coated Wheaten Terriers. Although pathogenesis of the disorder is incompletely understood, evidence suggests that food hypersensitivity and altered intestinal permeability develop first and that immune complex glomerulonephritis develops subsequently. The mode of inheritance has not been defined, but the disorder is common among Soft-Coated Wheaten Terriers, particularly in the United States where the condition is estimated to affect as many as 10-15% of the dogs of this breed. Females are affected slightly more often than males, and the average age when renal disease is diagnosed in affected dogs is 6 years of age. Clinical signs associated with the nephropathy include polyuria, polydipsia, vomiting, and weight loss. Laboratory findings include proteinuria, hypoalbuminemia, and hypercholesterolemia, often associated with abnormalities attributable to renal failure (azotemia, hyperphosphatemia, and non-regenerative anemia). The disease is complicated by thromboembolism in about 12% of cases, and hypertension occurs occasionally. By light microscopy, renal lesions are those of a membranous to membranoproliferative glomerulonephritis progressing to glomerular sclerosis accompanied by periglomerular fibrosis and secondary tubulointerstitial changes. Evidence of mesangial deposition of immunoglobulin A (IgA), IgM, and complement has been detected in the glomeruli of affected dogs using immunofluorescent labeling and electron microscopy.

Table 1 - Familial nephropathies in dogs and cats

Dogs **Renal dysplasia**

Lhasa Apso

Shih Tzu

Standard Poodle

Soft-Coated Wheaten Terrier

Chow Chow

Alaskan Malamute

Miniature Schnauzer

Dutch Kooiker (Dutch Decoy) Dog

Primary glomerulopathies

Samoyed kindred and Navasota kindred (X-linked)

English Cocker Spaniel (autosomal recessive)

Bull Terrier (autosomal dominant)

Dalmatian (autosomal dominant)

Doberman Pinscher

Bullmastiff

Newfoundland

Rottweiler

Pembroke Welsh Corgi

Beagle

Polycystic kidney disease

Bull Terrier (autosomal dominant)

Carin Terrier and West Highland White Terrier (autosomal recessive)

Amyloidosis

Shar Pei

English Foxhound

Beagle

Immune-mediated glomerulonephritis

Soft-Coated Wheaton Terrier

Burnese Mountain Dog (autosomal recessive, suspected)

Brittany Spaniel (autosomal recessive)

Miscellaneous

Basenji - Fanconi syndrome

German Shepherd - multifocal cystadenocarcinoma (autosomal dominant)

Pembroke Welsh Corgi - telangiectasia

Cats **Polycystic kidney disease**

Persian (autosomal dominant)

Amyloidosis

Abyssinian (autosomal dominant with incomplete penetrance, suspected)

Siamese and Oriental

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SPEAKER INFORMATION

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George E. Lees
Texas A&M University
College Station, Texas