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Familial renal diseases of dogs and cats
(Part 1 - 2)

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Renal failure occurring in a young dog or cat could be congenital, juvenile or familial. Congenital diseases are present at birth and due to either a genetic abnormality or a developmental abnormality due to the exposure to adverse factors in utero or the early neonatal period. Juvenile renal diseases are present at an early age but are not necessarily detectable at birth. Many, but not all, congenital and juvenile renal diseases are familial, or hereditary. Familial renal disease should be suspected when a group of related dogs or cats present with evidence of renal disease or when an individual animal of a particular breed presents with evidence of renal disease that is characteristic of a previously reported familial renal disease affecting that breed. Juvenile renal diseases have been reported in numerous breeds of dogs and cats, many of which a familial nature has been determined but the underlying genetic defect has been determined in only a few of the familial renal diseases. The age at presentation and rate of progression varies between the individual diseases. Furthermore, there may be considerable variation in the rate of disease progression in individual animals with the same disorder. Therapeutic interventions are usually focused on slowing the rate of progression and treating signs of uremia.

CLINICAL PRESENTATION

Most familial renal diseases in dogs and cats can be classified into 5 major categories: hereditary nephritis, amyloidosis, polycystic kidney disease (PKD), renal dysplasia and Fanconi syndrome. The clinical presentation of each of these differs. However, all of these diseases tend to be progressive leading to chronic kidney disease (CKD). Most of these diseases are characterized by an early age of onset of CKD, generally between 3 months and 3 years of age although some of these diseases can lead to CKD at a later age. For example, Dalmatians and bull terriers with hereditary nephritis have been reported to initially present with CKD as late as 7 and 10 years of age, respectively.

The clinical signs for which the affected animal presents are determined by the type of disease, the stage of CKD as well as individual variation. Stunted growth, weight loss and polyuria and polydipsia are some of the more common manifestations. Other signs may be vomiting, anorexia or decreased appetite, poor hair coat, malodorous breath, and diarrhea. When a young dog develops CKD, they often seem to manifest fewer signs than would be present in an older dog with a similar magnitude of azotemia. Physical examination findings in animals with advanced disease are often similar to those found in any animal with CKD (e.g., poor body condition, pallor, dehydration, oral ulceration). Fibrous osteodystrophy is sometimes found when a skeletally immature dog has developed advanced CKD. The kidneys of affected animals may be small or large, depending upon the specific disease and the stage of that disease.

Results of laboratory testing will vary with each disease. However, the familial renal diseases generally can be associated with one or more of the following abnormalities: azotemia, hyperphosphatemia, mild hypercalcemia, anemia, metabolic acidosis, decreased urine specific gravity, proteinuria or glucosuria. Ultrasonographic evaluation of the kidneys will often reveal nonspecific (e.g., loss of corticomedullary distinction, irregular cortical margins) and specific (e.g., multiple cysts of PKD) abnormalities.

The various familial diseases require different tests for definitive diagnoses. Furthermore, disorders that may produce similar signs need to be excluded. Few familial renal diseases have genetic tests available (e.g., PKD); others may require evaluation of a renal biopsy specimen (e.g., hereditary nephritis) to establish a diagnosis. Specific recommendations have been made for some of the diseases to allow for screening of seemingly healthy animals that are at risk (e.g., ultrasonography or genetic testing for PKD). The practitioner must have a thorough knowledge of the familial diseases and the breeds they impact, as well as an understanding of the appropriate means to establish diagnoses.

HEREDITARY NEPHRITIS

Hereditary nephritis (HN) refers to a diverse group of inherited glomerular diseases that are the result of a defect in basement membrane collagen (type IV). Defective collagen leads to premature deterioration of the GBM and progressive glomerular disease. HN is a differential diagnosis for any dog presenting with proteinuric renal disease, but particularly if the dog is young. HN has been reported in several breeds of dogs. An autosomal recessive form of disease occurs in English cocker spaniels, whereas bull terriers and Dalmatians develop an autosomal dominant form. An X-linked dominant form of HN has been described in Samoyeds and mixed breed dogs; carrier females may have mild disease. The report in the Samoyeds is of a single kindred; the disease is not considered to be common in this breed. HN is characterized by proteinuria, renal hematuria...
and progressive glomerular disease. Concurrent hearing and ocular abnormalities, as described in people with HN, appear to be uncommon in affected dogs.

HN result from genetic mutations or deletions in type IV collagen, which is the primary protein constituent of the GBM. The X-linked dominant disease of Samoyeds and mixed breed dogs is the result of a mutation in the COL4A5 gene encoding the α5(IV)-collagen chain. The autosomal recessive disease of English cocker spaniels is caused by a mutation in the COL4A4 gene encoding the α4(IV)-collagen chain. The exact genetic defect leading to the autosomal dominant form that has been described in bull terriers and Dalmatians has not been described but it appears that affected dogs may have a functionally defective α3-α4-α5 collagen network.

The presence of defective collagen leads to premature deterioration of the GBM and progressive glomerular disease. Prior to electron microscopic studies of English cocker spaniels, the renal lesions were described as renal cortical hypoplasia, or membranoproliferative or sclerosing glomerulonephritis. Electron microscopy is required to make the diagnosis of HN. There is multilaminar splitting and fragmentation of the GBM, often with intramembranous electron-dense deposits.

There is no specific treatment for affected dogs. Feeding a diet formulated for renal failure and administering angiotensin-converting enzyme inhibitors have proven beneficial in affected dogs. Early detection of HN by screening dogs of relevant breeds for microalbuminuria will allow early therapeutic intervention, which may slow disease progression. The rate of progression is predictable in Samoyeds and English cocker spaniels, with terminal renal failure generally developing before 2 years of age. However, disease progression is more variable in bull terriers and Dalmatians, with some dogs surviving for as long as 10 years.

AMYLOIDOSIS

Amyloidosis refers to a group of diseases where there is extracellular deposition of fibrils formed by polymerization of proteins that have a beta-pleated sheet conformation. Amyloidosis is one of the most common glomerular diseases in dogs. Renal amyloidosis is familial in the Chinese Shar Pei and possibly familial in beagles and English foxhounds. Amyloidosis is relatively uncommon in cats, except for the Abyssinian and Siamese (especially the Oriental shorthair colour variant).

Renal amyloidosis in Shar Peis develops at a mean age of 4.1 years, which is earlier than is seen in other dogs with amyloidosis. It is more common in females and is believed to be a recessive trait. Amyloid is usually deposited in the renal medulla. Because only 64% of Shar Peis have glomerular involvement, only 25-43% have proteinuria. Affected dogs may have signs of other organ involvement, particularly the liver. A history of recurrent fever (up to 41°C) and tibiotarsal joint swelling (called ‘Shar Pei fever’ or ‘Shar Pei hock’) may predate renal disease. Affected Shar Peis may be an animal model of Familial Mediterranean Fever (FMF) of people.

Abyssinian cats have amyloid deposited primarily in the medulla, resulting in medullary fibrosis, papillary necrosis and chronic kidney disease. Although glomeruli can be involved, marked proteinuria is uncommon. Siamese and Oriental shorthair cats may deposit amyloid in the liver, leading to hepatic rupture and hemorrhage. Diagnosis of renal amyloidosis in cats is based on a high index of suspicion and exclusion of other diseases or by post-mortem examination; biopsy of the renal medulla is not advised.

When the kidney is evaluated by conventional light microscopy, amyloid deposits in the glomeruli appear as acellular material that expands the mesangium and glomerular basement membranes and stains homogenously eosinophilic by hematoxylin eosin. Congo red staining can be used to confirm the diagnosis with conventional light microscopy.

The beta-pleated sheet configuration of amyloid fibrils leads to their insolubility and resistance to proteolysis, making specific treatment historically ineffectual. In people with FMF, colchicine prevents or delays renal amyloidosis, even in patients who continued to have recurrent febrile episodes. This has led to the recommendation that colchicine be used in Shar Peis with renal amyloidosis. This drug should be administered to Shar Peis shortly after recurrent fevers and swollen hocks are noted. Colchicine administration may lead to remission of proteinuria even after the appearance of amyloid deposits. There is no evidence to support that colchicine is effective once renal failure is present.

POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (PKD) has been described in adult male and female longhaired, Persian and Himalayan cats. The prevalence of PKD in Persian cats varies in different countries. PKD was reported in 16% of other breeds tested, including American Shorthairs, Siamese, American Curls, and Scottish Folds. PKD has also been reported in a number of breeds of dogs, including the bull terriers, beagle, Cairn terrier, West Highland White terriers, miniature poodle, and foxhound (single report); the diseases appears to be autosomal recessive in Cairn terriers and West Highland White terriers.

This disease is characterized by progressive development of fluid filled cysts within the renal medulla and cortex, which distort the normal renal architecture leading to enlarged and irregular kidneys. Cysts can be present in other organs as well (e.g., liver); hepatic involvement is common in Cairn terriers and West Highland White terriers. The number, size, anatomic location and appearance of the renal cysts varies among affected cats and dogs. The cysts tend to be larger in older cats. In people with PKD, interstitial inflammation and ultimately fibrosis is believed to be the primary mechanism of progression to end-stage renal disease. Chronic tubulointerstitial nephritis can be widespread in affected cats.

Genetic tests, which are available in the US and UK, is the best way to identify cats that carry this disease. Buccal mucosal swabs or EDTA blood can be collected from British shorthair and Persian cats as early as 8 weeks of age for this test. The next way to diagnose PKD in cats is via ultra-
sonography, which can be used to detect cysts as early as 8 weeks of age but the test is not 98% accurate until after 10 months of age. There is a large degree of phenotypic variability with this disease. Having the genetic defect or renal cysts does not predict the age of onset of renal failure. The average age of onset of renal failure in cats is 6 years. There is not a specific genetic test for affected dogs.

**RENA L DYSPLASIA**

The term renal dysplasia (RD) is applied to chronic renal disease of young dogs manifested by disorganized development of the renal parenchyma suggestive of abnormal differentiation. It has been reported in at least 23 breeds of dogs as well as the Persian cat. In some, a familial basis has been established. In other situations the term RD has been applied to animals because they developed CKD at an early age. Some of these diseases may be other familial diseases that need to be classified further.

Dogs with RD are often small relative to littersmates or compared with the breed standards and eventually develop renal failure and uremia, with death often occurring before 2 years of age. When examined by ultrasound, the dysplastic kidney frequently has an irregular contour, dilated pelvis, hyperechoic cortex and medulla and may contain cortical cysts; the renal cortex may be thin. Kidneys may develop a “dumbbell” shape. Fetal or immature glomeruli and persistent mesenchymal tissue are the hallmark histopathologic findings supportive of RD. Dilated renal tubules, renal fibrosis, cysts and interstitial inflammation may develop secondary to chronic and progressive renal disease. A linked DNA marker may identify carrier dogs and reducing the incidence of RD in Shih Tzus and Lhasa Apso s.

**FANCO NI SYNDROME**

Fanconi syndrome can be secondary to many renal insults; however, it is familial in the Basenji and Norwegian elkhound. Shetland Sheepdogs and Schnauzers may be predisposed. The disorder is caused by a partial defect in the proximal renal tubule and is manifested by reduced reabsorption of bicarbonate, glucose and filtered proteins. Affected dogs typically present with polyuria and polydipsia and glucosuria in the face of normoglycemia. The disease is progressive, with renal failure eventually developing. A metabolic screen of the urine is used to confirm the diagnosis (http://w3.vet.upenn.edu/research/centers/penngen).

The excessive loss of bicarbonate, potassium, calcium and phosphorous and the propensity to develop urinary tract infections necessitates frequent evaluations and prompt treatment of affected dogs. An apparently effective management protocol, often referred to as the Gonto protocol, has been distributed for affected Basenji dogs (http://basenjicompanions.org/health/images/Protocol12-003.html).

**MISCELLANEOUS DISORDERS**

A familial syndrome of protein-losing nephropathy (PLN) and protein-losing enteropathy (PLE) has been described in soft-coated wheaten terriers. The disease appears to be most common in the United States, where it has been estimated to affect upwards of 15% of the breed population although the exact prevalence in this breed remains undetermined. The mode of inheritance is unknown. The disease is slightly more common in female dogs. Disease onset is not detected until middle age (4-6 years of age). Affected dogs can have either glomerular range proteinuria or evidence of PLE; many dogs have both. Renal pathologic lesions are consistent with an immune mediated glomerulonephritis. Affected dogs have a high incidence of food allergies; while it is highly possible that the intestinal inflammation associated with the food allergies is the cause of the immune mediated glomerular disease, this hypothesis remains unproven. Effective management is aimed at antiproteinuric therapy for dogs that have PLN and dietary changes with or without immunosuppressive therapy for dogs that have PLE. Dogs that have combined PLN and PLE may be very difficult to manage, particularly when they are have advanced clinical presentations.

Membranoproliferative glomerulonephritis has been described in Bernese Mountain dogs and Brittany spaniels. Affected Brittany spaniels have a congenital deficiency of the third component of complement. The disease in Bernese Mountain dogs is believed to have an autosomal recessive mode of inheritance. Affected dogs are between 2 and 7 years of age at diagnosis and have signs compatible with glomerular disease.

Pembroke Welsh Corgies have been described with familial renal telangiectasia characterized by hematuria developing between 2 and 8 years of age. Hematuria appears to be episodic but can be severe enough to cause anemia. Hydronephrosis can develop secondary to obstructive calculi or blood clots.

**Further Reading**


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