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PROTEINURIA IN THE DOG AND CAT – 6 PAGES

This month my good friend and colleague Dr. Remo Lobetti from South Africa helps us decipher the clinical significance and origins of proteinuria. Dr. Lobetti speaks around the world on infectious disease and internal medicine and is one of the staple collaborators on the SonoPath.com project. For more on Dr. Lobetti go to [/www.sonopath.com/specialists_lobetti.asp](http://www.sonopath.com/specialists_lobetti.asp)

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INTRODUCTION

Protein losing nephropathy is a common but under diagnosed form of renal disease in the dog and cat. Unfortunately the disease is often clinical silent and can only be determined on urine analysis. Although evaluation of protein in the urine should be a standard diagnostic method, it is too rarely done. If diagnosed early, both the therapeutic options and the prognosis are much better. Urine analysis should be performed routinely in animals and all animals with an unexplained proteinuria should be thoroughly investigated as to the cause of the proteinuria.

The hallmark of glomerular diseases is abnormal protein loss in the urine. From a diagnostic standpoint the clinical finding of proteinuria must first be localized as pre-renal, renal, or post-rena

Pre-renal proteinuria

This is where protein loss occurs in the normal kidneys as a consequence of abnormal small molecular weight proteins present in the blood passing through the filtration barrier (e.g. haemoglobinuria, light-chain proteinuria in myeloma, myoglobinuria). Transient pre-renal proteinuria can result from increased intra-glomerular capillary pressure. The increased pressure favours transport of small proteins normally present in plasma through the filtration barrier, which may accompany strenuous exercise, fever, or seizures.

Renal proteinuria

Glomerular proteinuria occurs when there is disruption of the filtration barrier causing altered permselectivity and resulting in molecules normally retained within the plasma space being lost in the urine. Because albumin is relatively small (65,000 Daltons), it is the predominant protein lost from the glomerulus. The renal tubule can also result in proteinuria and occurs when the proximal tubule fails to reabsorb normally filtered proteins, which may be present in generalized tubulopathies such as Fanconi syndrome or acute tubular necrosis.

Post-renal proteinuria

Post-renal proteinuria occurs when protein enters the urine because of haemorrhage or inflammation within the lower urinary tract or genital tract.

Pre-renal proteinuria can usually be ruled out by history and with a normal serum protein and spinning the urine to distinguish haemoglobinuria and myoglobinuria from haematuria. Post-renal proteinuria can often be diagnosed on the basis of active urine sediment - haematuria, pyuria, and bacteruria.

GLOMERULAR STRUCTURE AND FUNCTION

The glomerulus is a tuft of highly branched capillaries, which together with Bowman's capsule form the renal corpuscle of the nephron. The glomeruli are confined to renal cortex. The components of the glomerulus include the capillary endothelial cells, the visceral epithelial cells, mesangial cells, mesangial matrix, and capillary basement membranes.

Glomerular capillary endothelial cells are similar to those in capillaries throughout the body except that they contain numerous large pores called fenestrae. Glomerular capillaries are covered by visceral epithelial cells called podocytes because they contain cytoplasmic foot processes that extend to the glomerular basement membrane (GBM). The spaces between the cytoplasmic foot processes are all called slit pores and they are covered with split pore membranes. This is where filtration is believed to occur. The visceral epithelium is covered with sialoprotein, which is negatively charged and tends to inhibit the passage of negatively charged macromolecules. The permselectivity of the glomerulus is thus both a charge- and sized-based barrier. Mesangial cells occupy spaces in the tuft between the capillary loops and produce the mesangial matrix. Mesangial cells have phagocytic capabilities. The mesangial matrix provides the structural support for the glomerulus. The GBM is located between the endothelial and visceral epithelial cells although it does not completely surround the capillary lumen.

GLOMERULAR INJURY

Glomerular injury is an important cause of renal disease in companion animals and appears to be more common in dogs than in cats. Because the components of the nephron are functionally interdependent, disease in the glomerulus if progressive and unresolved will eventually lead to damage to the tubules, interstitium, and vasculature, resulting in chronic renal failure.

In both dogs and cats, immune complex glomerulonephritis (GN) and amyloidosis are the most common primary glomerular disease syndromes. A hereditary susceptibility to certain types of GN has been demonstrated in humans but to date, not in dogs and cats.

Causative factors that are associated with GN in the dog and cat include the following:

- Infectious:
 - FeLV

- FIP
- Bacterial endocarditis
- Adeno virus
- Pyometra
- Ehrlichiosis
- Leptospirosis
- Chronic bacterial infections
- Inflammatory:
 - Pancreatitis
 - Systemic lupus erythematosus (SLE)
 - Chronic inflammatory skin disease
 - Polyarthritis
 - Chronic hepatopathies
 - Chronic gastro-enteropathies
- Neoplasia:
 - Lymphoma
 - Mast cell tumours
 - Other
- Metabolic/toxic:
 - Corticosteroids
 - Diabetes mellitus
 - Captopril
 - Pencillamine
 - Sulphonamides
 - Vaccines
 - Mercury
 - Bee stings
- Idiopathic
- Familial?

Potential mechanisms involved in glomerular injury include:

- Deposition of preformed circulating immune complexes into the GBM.
- In situ reaction of antibody with exogenous (planted) antigens or intrinsic glomerular antigens.
- Cell-mediated immune reactions.
- Complement-mediated damage.
- Deposition of amyloid protein.
- Haemodynamic forces (altered renal blood flow, systemic or glomerular hypertension).
- Hyperlipidaemia.
- Intra-renal coagulation.

Pathogenesis of glomerulonephritis

The most common inciting cause of GN is the deposition of preformed circulating immune complexes into the GBM. In certain instances immunoglobulins can combine with antigens previously planted in the GBM. Primary autoimmune GN occurs with antibodies reactive against native GBM proteins, but this has not been reported in companion animals. Any infectious, inflammatory, parasitic, neoplastic, or degenerative disease process that results in sustained antigenic stimulation can lead to immune-mediated glomerular

damage. However, in the vast majority of animal cases the antigen source or underlying disease process cannot be identified and the glomerular disease is thus labelled as idiopathic.

The presence of immune complexes in the GBM triggers a cascade of immunologic damage promoted by bioactive mediators (cytokines, nitric oxide, eicosanoids, complement, growth factors) that are either directly produced by glomerular cells or by recruited circulating blood cells, especially thrombocytes and neutrophils.

Because the inciting cause of glomerulonephritis is rarely known, it is usually characterized by its histological description:

- Membranous GN.
- Proliferative GN - increased glomerular cellularity.
- Membranoproliferative GN - combination of the above 2.
- Glomerulosclerosis - glomerular scarring associated with increased mesangial matrix deposition

Membranous GN is the most common type and is generally associated with heavy proteinuria and frequently an insidiously progressive course leading to renal failure. Membranoproliferative (mesangiocapillary) glomerulonephropathy is also common in the dog. Late stage membranous GN is difficult to definitively distinguish membranoproliferative GN without electron microscopy. Proliferative glomerulopathy generally presents with a fulminating course. Glomerulosclerosis is an end-stage of chronic inflammatory or degenerative renal diseases in which the glomeruli are replaced by hyaline or fibrotic material.

Amyloidosis

Amyloid is deposited mainly in the glomeruli, although in cats, it may be deposited in the interstitium of the medulla. Amyloid is produced by mononuclear-macrophage cells from amyloidogenic glycoproteins (serum amyloid protein A from hepatocytes in chronic inflammation and amyloid AL from the light chains of immunoglobulins in plasma cell dyscrasia). Glomerular amyloidosis can result in proteinuria, the nephrotic syndrome and ultimately renal failure. Medullary amyloidosis in cats produces no clinical signs but may cause renal medullary necrosis.

Consequences of glomerular dysfunction

Glomerular dysfunction can result in one or more of the following:

- Chronic renal disease.
- Moderate to severe protein losses can lead to negative nitrogen balance, hypoalbuminaemia, and culminate in the nephrotic syndrome.
- Drug metabolism may be affected as hypoalbuminaemia may alter drug metabolism by reduced binding and increased circulating levels of free drug.
- Hyperlipidaemia.
- Predisposition to thromboembolic disease because of increases in factors V, VII, VIII, and X; decreases in anti-thrombin III; and altered platelet function.
- Arterial hypertension is a common complication of glomerular disease and can affect as much as 80% of dogs with GN. The hypertension in turn promotes progressive renal damage.
- Low circulating levels of cholecalciferol and thyroxin may occur due to urinary protein loss.

DIAGNOSTIC APPROACH

All ages and breeds of dogs and cats may be affected with a higher incidence in animals over 5 years of age. In cats there appears to be a sex predilection as 75% of cases occurring in males and a slight breed predilection in dogs for Labradors, golden retrievers, and miniature schnauzers. Familial GN has been reported in the Doberman, Samoyed, Cocker spaniel, soft coat wheaten terriers, greyhound, Bernese mountain dog, Newfoundland, Rottweiler, and bull terrier. Familial amyloidosis is reported in the Abyssinian, Siamese, and Oriental Shorthair cats and Shar Pei dogs. Other dog breeds over-represented for amyloidosis are collies, beagles, and Walker hounds.

A careful history and full clinical examination are required because many cases of GN are secondary to occult disease. In one report of dogs with GN, approximately 50% of the dogs had a concurrent neoplastic, infectious, inflammatory, or immune-mediated disease at post mortem. Specific clinical abnormalities associated with glomerular injury may be subtle (weight loss, poor hair coat) or absent unless the animal is in renal failure. Oedema, ascites, or pleural effusion is present in animals with the nephrotic syndrome. Renal size may be normal, increased (amyloidosis, acute GN), or decreased (chronic GN or glomerulosclerosis). Haematuria with red blood cell casts may be evident in animals with GN.

Shar Pei dogs with amyloidosis may have pyrexia, swollen hocks, and/or a swollen muzzle. Clinical signs of hepatic involvement may be present in affected Shar Pei dogs and Abyssinian, Oriental Shorthair, and Siamese cats.

Occasionally animals may present with signs attributable to the thromboembolism: dyspnoea because of pulmonary thromboembolism and hind limb paresis from aortic thromboembolism. Some animals may present for acute blindness associated with hypertensive retinal detachment.

Persistent proteinuria with a negative sediment or accompanied by hyaline or granular casts on urine sediment is suggestive of glomerular disease. In early cases the urine dipstick may in fact be negative for proteinuria, as the concentration of protein is extremely low. This can be overcome by determining micro-albuminuria, which at this point is only available for dogs.

Animals with glomerular amyloidosis generally have the highest urine protein creatinine ratio. Animals with medullary amyloidosis may lack significant proteinuria early in the course of their disease.

Diagnostic workup

In summary a full investigation into the aetiology of renal proteinuria would include:

- History and full clinical examination
- Full urine analysis
- Haematology
- Urine culture
- Serum protein (albumin and globulin) levels with electrophoresis
- Serum urea and creatinine
- Urine protein-creatinine ratio and quantification of urine protein loss.
- ANA titre
- Abdominal ultrasonography
- Survey thoracic radiographs
- Serology or PCR (leptospirosis, toxoplasmosis, FeLV, FIV, Ehrlichia)
- Renal biopsy (histopathology, electron microscopy, and immunofluorescence).

MANAGEMENT OF GLOMERULONEPHRITIS

The ideal treatment plan for GN in dogs and cats is far from clear. Even when the histopathology type of GN is known based on a biopsy results; it is difficult to know the optimal treatment plan. Results of studies in human patients are, in many cases, conflicting. In some cases, therapies are shown to reduce proteinuria without improving survival. This seems paradoxical given the relationship noted in many studies

between magnitude of proteinuria and disease progression. One of the most aspects of therapy is to identify and correct any underlying disease process.

Very few studies of companion animal patients are published. When an underlying disease is found, correction of that disorder is often the most critical aspect of therapy. Unfortunately, such an underlying disorder is rarely found. Supportive care for patients with renal failure, hypertension, ascites, or oedema is always indicated.

High-quality, low protein diets have been recommended for many years because higher protein diets promoted a greater magnitude of proteinuria, which depleted the body albumin pool. Recently, the practice of protein restriction has been questioned in certain types of GN in humans. It may be that higher protein diets can be fed without inducing a greater magnitude of proteinuria if they are used together with an angiotensin-converting-enzyme (ACE) inhibitor or an anti-thrombin antagonist.

ACE inhibitors have been shown to reduce proteinuria in both dogs and humans with GN. In humans, improvements in lipid abnormalities (hypercholesterolemia, hyperlipoproteinaemia) are also clearly demonstrated.

Mini-dose aspirin is used routinely to minimize risks of hypercoagulability. Thromboxane inhibitors have been studied on a limited basis in dogs with some success and omega-3 fatty acids may also be of benefit.

Immunosuppressive therapy

The use of immunosuppressive agents, and which type, is perhaps the most controversial and difficult aspect of therapy for GN. Use of corticosteroids is indicated when an underlying corticosteroid-responsive disease is identified (e.g. SLE).

The current view is that idiopathic GN in humans does not appear too responsive to glucocorticoids, which contradicts early studies suggesting otherwise. In contrast, there is convincing evidence that cytotoxic therapy with cyclophosphamide or chlorambucil has benefit in idiopathic membranous GN, especially when instituted early in the disease. Other drugs that can be used are chlorambucil, cyclophosphamide, or cyclosporine. Many of the human studies evaluating chlorambucil also involved some months of treatment with pulsed methylprednisolone to reduce the risk of leukopenia from chlorambucil.

Best regards and special thanks to Dr. Lobetti for his article this month.

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