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CURRENT DATA REGARDING THE ETIOPATHOGENESIS OF GLOMERULAR AND TUBULAR DISORDERS ASSOCIATED WITH KIDNEY DISEASES IN SMALL ANIMALS: A REVIEW

DATE ACTUALE PRIVIND ETIOPATOGENEZA GLOMERULOPATIILOR SI TUBULOPATIILOR ASOCIATE BOLILOR RENALE LA ANIMALELE DE COMPANIE: RECENZIE

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ABSTRACT | REZUMAT

Renal diseases in companion animals are among the most frequently diagnosed pathologies, especially among the cat population. That is why early diagnosis and understanding of the pathological process, in terms of its manifestation and origin, is important. Renal pathologies can be classified according to a multitude of criteria, but the most used is according to the location of the pathological process. Thus, we can encounter glomerular, tubular, tubulo-interstitial, congenital, mechanical and vascular nephropathies. In dogs and cats, the most common glomerular diseases are proliferative (membranoproliferative glomerulonephritis, dense deposits disease-type I, proliferative glomerulonephritis (mesangial and endocapillary); extracapillary progressive glomerulonephritis; exudative glomerulonephritis (cystic and embolic) and non-proliferative glomerular diseases (amyloidosis, glomerulosclerosis, minimal change glomerulopathy, membranous nephropathy, hereditary nephritis - Alport syndrome, thin membrane disease). Tubulo-interstitial nephropathies are represented by renal tubular acidosis, Fanconi syndrome, renal glucosuria, nephrogenic diabetes insipidus, cystinuria, carnitinuria, hyperuricosuria and hyperxanthineuria.

Keywords: renal diseases, classification, companion animals

Afecțiunile renale la animalele de companie sunt printre cele mai frecvent diagnosticate, în special in rândul populației de pisici. De aceea este important diagnosticul precoce și înțelegerea procesului patologic, în ceea ce privește modul de manifestare si originea sa. Patologii renale pot fi clasificate după o multitudine de criterii, însă cea mai utilizată este localizarea procesului patologic. Astfel putem întâlni nefropatii glomerulare, tubulare, tubulo-interstitiale, vasculare congenitale și mecanice. La câini și pisici, cele mai frecvente boli glomerulare sunt: bolile proliferative (glomerulonefrita membranoproliferativă, boala depozitelor dense de tip I, glomerulonefrita proliferativă (mesangială și endocapilară); glomerulonefrita extracapilară progresivă; glomerulonefrita exsudativă (chistică și embolică) și bolile glomerulare neproliferative (amiloidoză, glomeruloscleroză, glomerulopatia cu modificări minime, nefropatia membranoasă, nefrita ereditară – sindromul Alport). Nefropatiile tubulo-interstițiale sunt reprezentate de: acidoza tubulară renală, sindromul Fanconi, glucozuria renală, diabetul insipid nefrogen, cistinurie, carnitinurie, hiperuricosurie și hiperxantineurie.

Cuvinte cheie: nefropatii, clasificare, animale de companie

The aetiology of renal diseases is variable, and the clinical manifestations are sometimes non-specific; therefore, in order to establish a diagnosis, it is necessary to use a wide range of clinical and paraclinical investigations, from simple urine sediment analysis to renal biopsy, immunofluorescence, electron microscopy, nuclear magnetic resonance, and procedures that combine the pictures from a positron emission tomography scan and a computed tomography. The increased frequency of these pathologies, especially in the cat population, makes the early recognition and specific identification extremely important in order to assure quality of life and prolong lifespan.

There is no unanimously accepted classification criterion for renal diseases in veterinary medicine, but the veterinary scientific community uses the World Health Organisation classification system created to define and standardise human renal diseases (6). This classification approaches the localisation criterion of the pathological process in order to expose and differentiate the aetiology, clinical manifestations and specific diagnostic methods.

Glomerular diseases are a group of dysfunctions of the renal parenchyma that affect the glomerular structures, having a multifactorial or unknown aetiology. Glomerular diseases mostly have an immunological origin and an incidence of 43% to 90% of the nephropathies diagnosed in dogs over 10 years old. Glomerular diseases are also diagnosed in cats, having a lower frequency in this species (12, 19, 36).

Proteinuria is the common sign of these kidney diseases, but until the clinical manifestations of renal failure, the initial cause, namely the glomerular injury, may remain undetected because the proteinuria decreases with the extension of the injury of the glomeruli, and the hypoalbuminaemia that appears as a re-

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sult of protein losses can be masked by dehydration (12, 21). In small animal veterinary medicine, the most common glomerular diseases are:

- proliferative glomerular diseases (membranoproliferative glomerulonephritis, dense deposits disease-type I, proliferative glomerulonephritis (mesangial and endocapillary);
- type II, crescentic glomerulonephritis or extracapillary glomerulonephritis with rapid progression);
- exudative glomerulonephritis (cystic glomerulonephritis, embolic glomerulonephritis);
- non-proliferative glomerular diseases (amyloidosis, glomerulosclerosis, minimal change glomerulopathy, membranous nephropathy, hereditary nephritis - Alport syndrome, thin membrane disease (3, 12).

PROLIFERATIVE GLOMERULAR DISEASES

Membranoproliferative glomerulonephritis

It is characterised by endocapillary proliferation and thickening of the glomerular basement membrane (GBM), being the most common glomerular disease in dogs with an average age of 5-6 years. It has a progressive character, being the main cause of chronic renal failure in dogs. It is most often immune-mediated, caused by infectious diseases, characterised by the deposition of immune complexes in the mesangium and in the walls of the glomerular capillaries, but there are also cases in which the appearance of lesions cannot be attributed to an antigenic stimulus, having an idiopathic origin (12, 21, 22, 26, 28, 29).

On histopathological examination, the lesions are global and diffuse; the glomeruli are enlarged, with significant mesangial proliferation and with the appearance of train tracks. Through the immunofluorescence (IF) technique, granular deposits represented by immunoglobulins (IgA, IgM and IgG) and the complement component 3 (C3) are seen in the mesangium or in the GBM (21, 30).

Membranoproliferative glomerulonephritis was associated with sulphonamide administration in Doberman dogs, with neoplasia, chronic inflammatory processes and infectious diseases such as chronic bacterial (brucellosis, mycoplasmosis), vector diseases (haemobartonellosis, leishmaniosis, borreliosis, babesiosis, ehrlichiosis, dirofilariasis), and viral (adenoviruses, herpesviruses, feline leukaemia, feline infectious peritonitis (FIP), feline immunodeficiency virus (FIV) but also with mercury and ethylene glycol poisoning (31). The appearance and evolution of glomerular lesions can also be the consequence of cardiovascular (hypertension, renal vein thrombosis) and metabolic diseases (diabetes mellitus).

There are two ways by which the immunological mechanism initiates damage to the glomerular structure:

a. deposition or capture of circulating immune complexes at the glomerular level, with mesangial or subendothelial localisation;

b. the formation of in-situ immune complexes when circulating antibodies react with antigens (of exogenous or endogenous origin) located at the glomerular level (12, 15, 21). Immune complexes cause a process of complement activation, neutrophilic and macrophage infiltration, platelet aggregation, with the release of inflammatory mediators and activation of a cascade of coagulation factors, as well as fibrin deposition (28, 33).

Dense deposit disease

It is rare and is characterised by deposition of complement in the GBM and mesangial matrix. It has long been considered a subtype of membranoproliferative glomerulonephritis (12, 38). The pathogenesis of this disease involves an uncontrolled systemic activation of complement by the so-called nephritic factor, which is a serum IgG. The anatomopathological changes are similar to those in membranoproliferative glomerulonephritis only in a limited number of cases and are manifested by endocapillary thickening and proliferation. The immunofluorescence technique highlights the presence of linear complement deposits in the capillary walls, without the presence of immunoglobulins. Under the electron microscope (EM) these complement deposits appear as dense bands in the middle of the GBM and in the mesangial matrix (38).

Proliferative glomerulonephritis

It is caused by endocapillary or mesangial proliferation, with an incidence of 2-16% of all glomerular diseases (19).The patients in which this nephropathy was reported had an average age of 7 to 9 years, with clinical signs of proteinuria and renal failure in various stages. The pathogenetic mechanism is immune-mediated, being the consequence of short-term diseases, whose clinical signs remit until the appearance of glomerular damage, with persistent infections usually leading to the evolution of membranoproliferative glomerulonephritis and membranous nephropathy.

Histologically, proliferative glomerulonephritis manifests as a mesangial proliferation with a marked increase in the number of cells in its structure, accompanied by endothelial proliferation and infiltration of inflammatory cells. Glomeruli appear enlarged, and capillaries have thin basement membranes and flattened lumens. Through IF and ME, fine granular deposits of IgA and IgM are observed in the GBM and in the mesangium, but IgG and C3 can also be observed (5, 12).

IgA nephropathy or Berger's disease

In human medicine, it is associated with the proliferation and expansion of the mesangial matrix and is a glomerulonephritis characterised by mesangial deposits of IgA. For a definite diagnosis of the condition, immunofluorescence (IF) is used, showing the predominance of IgA deposits, along with IgM, IgG and C3 deposits. In dogs, the highest incidence of IgA nephropathy was found in gastrointestinal and liver diseases and food allergies, as a result of the excessive production of immune complexes and their deficient clearance, associated with hepatopathies (12).

In humans, the nephropathy is found in young patients. In dogs, it is recorded at an average age between 4 and 7 years, accompanied by episodes of hae-

maturia, proteinuria and signs of renal failure.

Extracapillary or rapidly progressive glomerulonephritis is rarely encountered in dogs, characterised by extracapillary proliferation and fibrinoid necrosis in most glomeruli, with the formation of crescentic epithelial deposits in Bowman's space, with a rapid evolution towards chronic renal failure and death. The deposit consists of epithelial and inflammatory cells arranged in layers; the underlying glomeruli are compressed and show lesions of fibrinoid necrosis (22, 40).

Exudative glomerulonephritis

Cystic glomerulonephritis is a very rare nephropathy in dogs and cats. The necropsy aspects reveal a slight increase in volume of the kidney, a grey colour, and a spongy appearance due to the presence of small cysts. Histologically, there is an increase in the volume of the renal corpuscles as a result of the accumulation of a sero-fibrinous exudate, which over time causes atrophy of the glomerular capillaries, periglomerular and interstitial fibrosis. The clinical signs are of chronic renal failure (32).

Embolic or purulent glomerulonephritis occurs in septicaemia and is caused by the deposition of pathogens at the level of glomerular capillaries, with the appearance of multiple foci of inflammation and micro abscesses. Nephropathy can also develop, affecting the extra-glomerular tissue. Histologically, there is the deposition of bacterial colonies at the glomerular level, necrosis and neutrophilic infiltration that can obliterate the glomeruli (18).

Non-proliferative glomerular diseases

Among non-proliferative glomerular nephropathies in companion animals, amyloidosis is most often diagnosed.

Renal amyloidosis consists of the deposition of non-functional proteins (amyloid) in the glomeruli. Amyloid is made up of proteins of plasmatic origin that have the particularity of forming insoluble fibrillar structures through incorrect polymerisation in beta-folded configuration (22, 39). Amyloid fibrillar proteins have different compositions depending on the type of amyloid and the clinical form. According to the distribution of deposits, amyloidosis can be systemic or localised, and depending on their structure, it is AL (primary) and AA (secondary).

Dogs are domestic animals most frequently affected by amyloidosis, which has an incidence of up to 25% of all glomerular diseases. AA amyloidosis, reactive or secondary, is the most common form, evolving on average at over 9 years of age. Females have a higher incidence of the disease, and the most susceptible breeds are the Beagle, Collie, and Treeing Walker Coonhound. Clinical signs are characteristic of glomerulopathies, although other organs (liver, spleen) can be affected, but symptoms characteristic of amyloid deposition at their level are rare. Chronic inflammatory processes of infectious or non-infectious origin together with neoplasia, that often evolve asymptomatically, have been associated with secondary amyloidosis in a proportion of 32-52%.

In the Shar-Pei breed, amyloidosis can be hereditary and is usually diagnosed on average at 4 years of age. The amyloid is often located at the medullary level and only in 64% of cases at the glomerular level; therefore, proteinuria may be absent. Many patients present episodes of recurrent fever, and inflammation of the tibio-tarso-metatarsal joints, as well as damage to other organs, especially the liver. The hereditary character is also supported by statistics that show that 25-50% of the descendants of dogs suffering from this condition will show clinical signs of the disease in adulthood (11, 39).

In cats, this nephropathy is rare, with the exception of the Abyssinian breed. The amyloid is deposited mainly in the medullary region but also at the glomerular level. Specific localisation of the amyloid causes medullary fibrosis and papillary necrosis, which lead over time to chronic renal failure (12). In the Siamese breed and other short-haired breeds, the deposition of amyloid occurs predominantly at the hepatic level.

The pathogenetic mechanism of this nephropathy involves constantly increased levels of serum amyloid A (SAA) - an acute phase protein, which is produced by the liver, as a result of the stimulation of hepatocytes by the cytokines (IL-1, IL-6) released in the event of tissue damage (1, 14). Although many animals suffer from chronic inflammatory processes, only a small part of them end up being affected, a fact that also supports the involvement of genetic factors in the appearance of the disease.

On necropsy, the kidneys appear pale, hardened and slightly reduced in volume. Under the optical microscope, amyloid deposition is observed on both sides of the GBM, in the vessel walls, tubular basement membranes and in the interstitium.

Renal biopsy is necessary to differentiate amyloidosis from other glomerular nephropathies, but it is not recommended due to the friability of the organ. A diagnostic test, however, can be used by administering Congo red i.v., 0.08 g/kg, 1% solution; after one hour, blood is drawn. If the plasma discolours within one hour at most, the test is positive (34).

Glomerulosclerosis is most often encountered in the final stages of glomerular damage. The prevalence of this disease increases with age and can appear as a primary condition, such as the segmental focal form, which has genetic, hereditary, or secondary implications in persistent, undiagnosed hypertension (8, 12, 16). It is a nephropathy frequently encountered in human patients with diabetes, a lesion that also occurs in animals diagnosed with this disease.

Focal and segmental glomerulosclerosis is a disease that has been identified in the dog but for which few data exist, and the clinical relevance is incompletely documented. The term "focal" in the name of the disease refers to the damage of a limited number of renal corpuscles (Bowman's capsule and the vascular glomerulus), and "segmental" means the damage of a part of the involved renal corpuscle. It is characterised by asymptomatic proteinuria, which can be misdiagnosed as membrano-proliferative glomerulonephritis. On histopathology, three types of lesions are

observed: cellular alteration, initially podocytic, hyaline deposits and sclerosis. Through the IF technique, immunoglobulin and C3 deposits can sometimes be observed in areas with sclerosis (12).

Minimal change glomerulopathy is a rare condition in dogs and cats but is a common cause of nephrotic syndrome in human patients, especially children. Since EM is required for a definite diagnosis, it is most likely often misdiagnosed. In animals, especially in dogs, it is found secondary to *Ehrlichia canis* infection and after the administration of Mastinib, a tyrosine-kinase inhibitor, used in anti-cancer therapy (21). Isolated cases of the disease have been described in the USA, manifested by proteinuria, rarely also evolving with nephrotic syndrome. The pathogenic mechanism involves the production of lymphokines by dysfunctional T lymphocytes that affect the selective filtering capacity of GBM, leading to proteinuria and hypoalbuminemia. Under the optical microscope (OM), no change is observed, hence the name, instead in EM there are mesangial proliferations, vacuolisations, damage to the podocyte processes (foot process) and the appearance of microvilli at the level of the visceral epithelial layer. The IF technique did not identify the deposition of immune complexes (12, 15).

Membranous nephropathy (ME) is the most common glomerulopathy diagnosed in cats, with other types of glomerulopathies being rare, and the second most common in dogs. Because glomerular and interstitial inflammatory processes are rarely evident, this nephropathy is a glomerulopathy rather than a glomerulonephritis. Clinically, it has a high incidence in males, being more common in cats with an average age of 3.6 years. It is manifested by severe proteinuria, with nephrotic syndrome and signs of renal failure, many of the cats presented at the consultation having normal or enlarged kidneys (12). The pathogenesis of this disease involves structural alterations produced by immune complexes. In primary or idiopathic membranous nephropathy, the immune complexes are found in the subepithelial space of the glomerular vascular bundles, while in secondary membranous nephropathy the immune complexes are found in the mesangium or subendothelial space, or even in the subepithelial space (12, 18, 28, 33). This condition is also found as a familial disease in the Doberman pinscher breed.

Hereditary nephritis has been diagnosed in various dog breeds with autosomal recessive transmission in the English Cocker, autosomal dominant in the Bull Terrier and Dalmatian, and X-linked in the Samoyed and its crossbreeds. Hereditary nephritis, or Alport diseases, as it is named in human medicine, is an X-linked hereditary nephropathy found in male Samoyeds, initially presenting at 2-3 months of age with proteinuria and glucosuria, continuing with uraemia from 6 to 9 months, and progressing to kidney failure. The disease can also manifest itself in females (transmission being autosomal recessive) through proteinuria at the age of 2-3 months, without other signs of renal failure, but not reaching normal body development. The genetic defect in this case is the mutation of a gene involved in the synthesis of collagen IV, a constituent of GBM. It is made up of 3 α chains, which in turn are of 6 types, encoded by 6 genes COL4A1-COL4A6, the mutant gene being CO LA5 (4, 12). This mutation alters the structure of this collagen, and renders it highly susceptible to enzymatic proteolysis, with proteinuria and progressive renal disease resulting from GBM damage.

Eye disorders, common in human patients, may also occur rarely in animals. Bull Terriers may present anterior lenticonus—bulging of the lens and the underlying cortex. On histological examination, cortical hypoplasia, membranoproliferative lesions, and glomerular sclerosis are observed through MO. ME reveals GBM fragmentation, which takes on a laminated appearance, and areas with electron-dense granules.

Hereditary nephritis in the English Cocker Spaniel breed is caused by mutations of the COLA3 and COLA4 genes, manifesting both in adults and in females aged between 6 and 24 months. Clinically, it is characterised by proteinuria, then azotaemia and delayed body development. The histological lesions are similar to those of hereditary nephritis affecting the Samoyed breed (12).

TUBULO-INTERSTITIAL NEPHROPATHIES

These nephropathies are pathological processes that affect the renal proximal and distal tubules. The renal tubes are responsible for the absorption of various blood components that have been filtered at the glomerular level, for the elimination of some electrolytes, drugs and maintaining the hydro-electrolytic balance.

Renal tubular acidosis

It is a rare tubular nephropathy manifested by hyperchloremic metabolic acidosis, being found in acute kidney diseases and in stages 2-4 of chronic renal failure. Several types of tubular acidosis have been described, depending on the tubular portion affected.

Proximal tubular acidosis

It occurs as a result of a defect in sodium bicarbonate reabsorption at the level of the proximal convoluted tubule, which is 95% reabsorbed at this level. It can appear as a single pathological entity or, more frequently, be accompanied by other reabsorption defects of different ions and constituents of primary urine, such as glucose, Na^+, K^+, phosphates, uric acid and amino acids, a situation encountered in the case of Fanconi syndrome. Proximal tubular acidosis can have genetic causes, namely a defect in the sodium bicarbonate cotransporter in the basolateral membrane of the proximal convoluted tubule, or it can occur secondary to the administration of some drugs and the consumption of some toxic substances.

As a result of this filtration defect, the serum level of bicarbonate decreases with the increase in urinary excretion, a self-limiting pathological condition; however, since as the serum level of bicarbonate decreases, the amount that can be reabsorbed is also re-

duced, later reaching a level at which the tubule proximal can completely absorb bicarbonate. Administration of parenteral or enteral bicarbonate does not resolve this state of metabolic acidosis, leading not only to increased excretion of bicarbonate but also potassium through the urine. The indicated therapy consists of reducing sodium in the diet and administering diuretics. To combat acidosis, potassium citrate can be administered under strict supervision so as not to cause hypocalcaemia. The diagnosis of proximal tubular acidosis is based on hyperchloremic metabolic acidosis, urinary bicarbonate elimination rate of more than 15% after correction of systemic acidosis with alkaline solutions, acidic pH of urine <6 (excluding lower urinary tract infections), with a normal glomerular filtration rate (35).

Distal tubular acidosis is manifested by the inability of the kidneys to acidify the urine despite systemic metabolic acidosis, as a result of deficient tubular secretion of the H^+ ion. The mechanisms of this deficit could be: disruption of the pump that secretes K^+ (classic distal form), passage of increased amounts of H^+ (secreted) from the lumen to the tubular cells (gradient defect), the decrease in the electro-negative potential difference in the lumen, which promotes the secretion of H^+ (voltage-dependent form) and insufficient amount of $NH4^+$ at the level of the distal tube. The reduced amount of H^+ causes a decrease in $NH4^+$ and, at the same time, a decrease in the excretion of total acids. The causes incriminated are genetic, with autosomal dominant transmission, autoimmune, obstructive, as well as renal transplantation. Among the complications of this condition are: nephrolithiasis (with calcium phosphate or struvites), nephrocalcinosis (resulting from alkaline urine pH and decreased urinary citrate concentration), bone demineralisation and excessive excretion of potassium through urine.

The diagnosis is based on metabolic acidosis, urinary pH <6, as well as the ammonium citrate test. The test involves oral administration of 110 mg/kg ammonium citrate and urine pH testing before the procedure and hourly for 6 hours after administration. In normal dogs, a reduction in pH is observed to 5, and in cats to 5.5. In cats, distal tubular acidosis has also been encountered in pyelonephritis caused by *E. coli*, in urinary tract infections, as well as in acute ischaemic renal failure (25).

Fanconi syndrome

It is a generalised dysfunction of the proximal tubule characterised by excessive urinary elimination of amino acids, low molecular weight proteins, glucose, bicarbonate, calcium phosphates, magnesium, uric acid, sodium, potassium and water. The pathogenetic mechanisms suspected to be involved are represented by the insufficient capacity of the tubular cells to produce the necessary energy to transport various compounds or their deficient absorption. More than 70% of reported cases of Fanconi syndrome in dogs have been registered within the Basenji breed, of which 10-30% of specimens of this breed end up clinically expressing the disease in adulthood, being considered a hereditary nephropathy. Idiopathic Fanconi syndrome is also found sporadically in dogs belonging to other breeds such as: Labrador Retrievers, Yorkshire Terriers, Shetland Sheepdogs, Border Terriers and mixed breeds, in which it manifests between the ages of 10 weeks and 11 years (7, 24). Secondary occurs following gentamicin administration, ethylene glycol ingestion, and in primary hypoparathyroidism associated with hypovitaminosis D (7). The diagnosis is made through biochemical analyses of blood and urine, observing glucosuria with normal blood glucose, isosthenuria, aminoaciduria, hyperphosphaturia, hypophosphoremia, hypokalaemia and hyperchloremia, with increased levels of creatinine and urea as the disease progresses (7).

Renal glucosuria

It is a congenital condition of the proximal tubule that is manifested by a low renal threshold for glucose, with glucosuria and normal blood glucose, constituting, in some cases, the first clinical sign for Fanconi syndrome. Affected animals may be asymptomatic or may present, as a result of persistent glucosuria, polydipsia, polyuria, as well as urinary tract infections due to bacterial colonisation in the presence of glucose (5, 12). Primary renal glycosuria is rare but has been reported in the Scottish Terrier, Norwegian Elkhound, and their crossbreeds. The diagnosis is made through serial determinations of blood glucose, the dosage of serum fructosamine, and the differential is made with the early stages of Fanconi syndrome (12).

Nephrogenic diabetes insipidus (NDI)

NDI is a rare condition that occurs as a result of the lack of response of the kidneys to the antidiuretic hormone (ADH). ADH is produced by the hypothalamus and has the property of attaching to the receptors of the basolateral membrane of the collecting tubules, stimulating water reabsorption in the distal tubule and collecting ducts. In NDI the specific receptors do not respond to the action of ADH. Acquired NDI occurs as a result of interference with the attachment of ADH to receptors due to toxins (endotoxins produced by *E. coli*), drugs (glucocorticoids, chemotherapy), metabolic and endocrine disorders (Cushing's syndrome, high aldosterone levels, hypercalcemia, hypokalaemia), pyelonephritis and polycystic kidney disease (12, 13).

Congenital NDI is caused by ADH receptor deficiency and manifests shortly after birth, with affected animals usually diagnosed in the first year of life. The symptomatology encountered is characterised by polyuria/polydipsia, hyposthenuria, sometimes dehydration, hydro-electrolytic disorders, weakness and, in more serious cases, even neurological signs: disorientation, tremors, convulsions and collapse.

The most informative test is the ADH response (more reliable than the water restriction test). Administer 2-4 drops of desmopressin (ADH) into the conjunctival sac of the animal, the specific gravity of the urine being determined before administering the product; the bladder is emptied at 2 hours, and the speci-

fic gravity is determined at 4, 8, 12, and 24 hours. In animals with central diabetes insipidus, the specific gravity of urine reaches normal limits during the test, whereas in animals with NDI, no major fluctuations of urinary specific gravity are observed. It can also be done at home by the owners, during 3-5 days. Desmopressin is administered once a day in the conjunctival sac; in the case of central diabetes insipidus, the owner is able to observe a reduction in water consumption and the frequency of urination, or no change in the other forms of diabetes insipidus (8, 13).

Cystinuria

It is a hereditary defect of the proximal convoluted tubule manifested by tubular reabsorption and deficient digestive absorption of some dibasic acids, including cystine. Cystine is an amino acid insoluble in urine, and most of the time this nephropathy results in urolithiasis. The exact nature of this tubular defect is believed to be a deficiency in cystine transporters. Some breeds only lose cystine through the urine, while others have deficient reabsorption of other amino acids such as ornithine, lysine and arginine.

Epidemiological studies have shown that this tubular defect occurs more frequently in males, the most prone breeds being the Terra Nova, Mastiff, Staffordshire Bull Terrier, Bulldog, and Basset Hound. Hereditary transmission is sex-linked or autosomal recessive (12). The autosomal recessive form, or type I, found in the Terra Nova breed is caused by the gene mutation that causes the disease in human patients as well, with stones forming at a young age in both males and females. On the other hand, in other breeds it is observed only in uncastrated males, the transmission being sex-linked, the concentration of cystine in the urine having a moderate level, with the formation of stones at older ages (17). The symptoms are common to urolithiasis, encountering dysuria, pain when urinating, haematuria with foul-smelling urine, and renal colic accompanied by the attitude of lumbago with an average age of 4.8 ± 2.5 years (15, 17).

The diagnosis is made on the basis of clinical signs, breed predisposition, as well as by analysing the urine sediment. The University of Pennsylvania has developed DNA tests to identify carriers of the mutated gene for the Terra Nova and Labrador breeds.

Carnitinuria

It is characterised by excessive excretion of carnitine in the urine. It is also found in specimens with cystinuria, in chronic renal failure, following prolonged treatment with steroid anti-inflammatory drugs, as well as in urea cycle disorders. Persistent carnitinuria can lead to dilated cardiomyopathy, with carnitine having a role in cardioprotection and as a transporter of short-chain fatty acids through membranes, used for energy production (12).

Hyperuricosuria

It is characterised by excessive excretion of uric acid in urine. This metabolic deficiency has an autosomal recessive transmission and over time leads to the formation of urinary stones. Uric acid results from the degradation of nucleic acids, representing the final product of purine metabolism in humans, monkeys and Dalmatian dogs. In other mammals allantoin represents the final metabolite. Uric acid is reabsorbed in the renal tubules, except in Dalmatian dogs that have completely lost the ability to reabsorb urate, and in which excretion is equal to or greater than the glomerular filtration rate of the metabolite. Although this metabolic defect is present in all specimens of this breed, not all individuals show urolithiasis and the associated clinical signs. Recent studies have identified the cause of this metabolic anomaly in Dalmatians, consisting of a mutation of a transporter of uric acid, SLC2A9, at the level of the proximal tubule, closely related to genetic selections made by breeders for hair colour and spot pattern (Bannasch et al., 2008). Hyperuricosuria also occurs in primary liver diseases, where the conversion rate of uric acid to allantoin decreases due to uricase deficiency (12).

Hyperxanthinuria

It occurs as a result of the deficiency of xanthine oxidase, which transforms xanthine, an organic compound derived from purine, into uric acid. As a result of this deficiency, xanthine stones may appear.Most affected dogs are treated with allopurinol, a xanthine oxidase inhibitor administered to patients with urate urolithiasis who are not on purine dietary restrictions. The congenital form was found in the King Charles Cavalier and Dachshund breeds, the wire-haired variant (12).

CONCLUSIONS

The renal diseases that are most frequently diagnosed in companion animals originate in the glomerulus, leading to specific requirements for the follow-up and the treatment of the patients. Advances are made in the field of veterinary uro-nephrology that help clinicians in making more precise and early diagnostics of these pathologies and also provide better care and treatment plans.

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