Common Geriatric Disease of Dogs

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Introduction

Aging is an intrinsic systemic process that affects all cells, tissues, and organs of the body resulting in altered homeostasis, decreased ability to respond to environmental stimuli, increased frailty, and predisposition for illness. Therefore geriatric populations are at increased risk for the development of systemic abnormalities including multiple organ abnormalities as well as a population more commonly receiving long-term or multiple medications. Although many factors contribute to the aging process (genetics, nutrition, and environmental factors) each species and individuals within a species age differently.

The classification of geriatric varies with species and in dogs varies between breeds. In addition, each species has their own unique group of chronic diseases that require routine monitoring for early disease recognition, long term management, and to decrease the risk of adverse clinical events. The more common chronic disease of geriatric canines will be reviewed focusing on diseases that have a significant impact on drug disposition (chronic kidney disease, chronic liver disease, and cardiovascular diseases), diseases that can be more difficult to definitively diagnose in geriatric patients (endocrinopathies – hypothyroidism and hyperadrenocorticism), and a brief discussion focusing on osteoarthritis which can be a pharmacological challenge in the geriatric patient.

Chronic Kidney Disease

The inherent age-related structural and physiological changes in the functional nephron result in an overall decrease in the renal reserve. Structural changes associated with age in humans include glomerulosclerosis, mesangial expansion, obliteration of juxtamedullary nephrons, dysfunction of autonomic vascular reflex, and tubule-interstitial changes. These structural changes result in altered renal physiology in older adults including decreased glomerular filtration rate (GFR), altered tubular handling of creatinine, reduced sodium reabsorption, and reduced potassium secretion. These age-related changes in the kidney make elderly adults more likely to experience clinical adverse events in association with standard levels of stimuli (stress or illness) and therapeutic dosage regimens. Studies are lacking in our veterinary species but likely these age-related structural and physiological changes also occur in the kidneys of dogs with age, making the geriatric canine more susceptible to clinical decompensation in association with clinical stresses.

Despite the similarities in the loss of kidney reserve and decreased GFR associated with the aged-kidney and patients with chronic kidney disease (CKD) there are important clinical differences between these two populations. In the “otherwise healthy” aged-kidney the function of the proximal tubules is preserved and serum erythropoietin levels and hematocrit are maintained. In addition serum urea, electrolytes (magnesium, calcium, phosphorus), vitamin D, and parathyroid hormone levels remain normal in the patient with an aged-kidney. Two important clinical consequences of hypofiltration of the aged-kidney patient are their risk of developing volume overload following a sodium load and the need for drug dosage adjustments based on a decrease in GFR.

The prevalence of chronic kidney disease (CKD) increases with age and in geriatric patients CKD is more often associated with irreversible nephron loss, fibrosis, and progressive disease. Irrespective of the inciting cause the common histopathological changes associated with CKD are non-specific and include tubular loss with associated fibrosis and mineralization, glomerulosclerosis and
glomerular atrophy. Inflammatory changes are localized to the interstitium with mononuclear cells (small lymphocytes, plasma cells, macrophages) being the dominate cell types present.

In many geriatric patients subclinical CKD commonly persists without detection because of the large functional reserve of the kidney, compensatory hypertrophy of remaining functional nephrons, and the relatively insensitive markers of kidney function routinely available. When 66% of the kidney’s nephrons are lost the term renal insufficiency is sometimes used as the kidneys have lost their ability to produce concentrated urine but the kidney maintains the ability to excrete wastes. As nephrons are lost the remaining functional nephrons increase fluid excretion per nephron preventing the development of clinical signs. Therefore renal insufficiency is commonly not clinically identified as these patients feel well despite being persistently isosthenuric, polyuric, and polydipsic, although not azotemic. It is not until 75% of the nephrons are lost that kidneys ability to excrete wastes becomes compromised and patients develop azotemia. As the GFR of the kidney decreases the clinical sequela of CKD begin to emerge including uremia, hyperphosphatemia, metabolic acidosis, systemic hypertension, anemia, and secondary hyperparathyroidism.

In older dogs CKD is most commonly acquired due to nephron loss as a consequence of aging or a result of a primary kidney insult of known or unknown etiology. The more common underlying causes for CKD in dogs include infectious triggers (pyelonephritis (E. coli), leptospirosis), dehydration or hypovolemia, nephrotoxic drugs (NSAIDs, aminoglycosides, amphotericin B, cisplatin), glomerular disease, and neoplasia. Glomerular disease and associated proteinuria is a significant contributor to progressive CKD in dogs. Excessive protein that crosses the glomerular capillary accumulates in the glomerular tuft resulting in mesangial cell proliferation. Excessive protein in the glomerular filtrate is toxic to tubular epithelial cells triggering interstitial inflammation and fibrosis leading to progressive nephron loss. Glomerular disease in dogs develops secondary to underlying chronic systemic diseases including infections (Ehrlichiosis, Leptospirosis, Borreliosis, chronic bacterial infections, heartworm disease, Brucellosis) and non-infectious inflammatory diseases (inflammatory bowel disease, systemic lupus erythematosis, hyperadrenocorticism) and neoplasia.

In many cases the inciting underlying cause for nephron loss is usually unknown therefore the management of CKD focuses on reducing the workload of the kidney, controlling clinical signs, and preventing and/or treating complications. Medical management of CKD begins with the pursuit of appropriate diagnostic work-up to stage the disease and identify any known or suspected underlying causes. CKD is staged according to the guidelines developed by the International Renal Interest Society (IRIS). Staging is based on renal function (serum creatinine), proteinuria, and blood pressure. Any identified sequela (dehydration, positive urine culture, hypertension, proteinuria, hyperphosphatemia, gastrointestinal ulceration, anemia) should be appropriately treated and monitored. In addition protein, phosphorus, and sodium reduced kidney diets are recommended and the discontinuation and/or avoidance of any nephrotoxic therapies (NSAIDs, aminoglycosides, amphotericin B, cisplatin) are also recommended.

**Chronic Liver Disease**

The common physiological changes in the hepatobiliary system with age are a decrease in the numbers of hepatocytes and an increase in hepatic fibrosis. Interestingly, based on human studies, overall liver function is well preserved with age. The liver is uniquely placed between the portal and systemic circulation and the primary organ responsible for the metabolism of endogenous and exogenous substances, therefore with a progressive loss of liver function comes the risk for adverse clinical events. The more common causes of chronic liver disease in dogs include inflammatory hepatitis, infiltrative hepatopathies, and hepatic fibrosis and cirrhosis.

**Chronic inflammatory hepatitis** in dogs can be triggered by infections (bacterial – leptospirosis vs viral – infectious canine hepatitis), drugs (long-term anticonvulsant therapy or NSAIDs), copper accumulation (commonly a familial predisposition – Bedlington terrier, West Highland white terrier, Doberman pinscher, Cocker spaniel, Labrador retriever), or associated with an immune-mediated origin.
Despite the underlying cause inflammatory hepatitis in dog begins with hepatic necrosis followed by the subsequent infiltration of inflammatory cells (macrophages, lymphocytes, and plasma cells) and fibrosis. Chronic hepatitis is generally a slow but progressive disease ultimately ending in cirrhosis. Biochemistry changes begin as primarily a hepatocellular pattern followed by the development of a cholestasis and progressive loss of liver function. The diagnosis of inflammatory hepatitis is supported by imaging and definitively diagnosed by liver biopsy including histopathology and copper quantification.

Treatment targets the underlying cause if identified but more commonly treatment is focused on preventing or slowing the development of liver dysfunction. Supportive therapies include antioxidant supplementation (vitamin C, vitamin E, silymarin), supplementation with a glutathione source (S-adenosyl-L-methionine, N-acetylcysteine), and in cases with non-obstructive cholestasis the use of ursodeoxycholic acid to stimulate bile flow. More specific supportive therapies are based on the results of liver biopsy findings include copper chelation (D-penicillamine, zinc acetate), antifibrotics (cholchicine, prednisone), and immunosuppressive/anti-inflammatory therapy (prednisone, azathioprine).

**Infiltrative neoplasia of the liver** can either be tumors of primary hepatic origin (epithelial vs. mesodermal or benign vs malignant), metastatic carcinomas or sarcomas (common sites of origin include pancreas, spleen, adrenals, or gastrointestinal tract), and hemolymphatic tumors. A liver biopsy diagnosis is necessary to define the tumor type and direct medical versus surgical therapeutic recommendations.

**Cirrhosis** is the final common pathway to many chronic hepatopathies in dogs and associated with fibrosis and end-stage liver disease. Unfortunately, dogs with normal liver enzymes can still have severe underlying liver injury, including dog with cirrhosis. Dogs with hepatic cirrhosis often have associated liver dysfunction and clinical signs including hypoalbuminemia, portal hypertension, ascites, acquired portosystemic shunts, and hepatic encephalopathy. Imaging can often be suggestive of cirrhosis but a liver biopsy is needed to definitively diagnosis the presence of fibrosis and cirrhosis.

Treatment of any identified underlying triggers is recommended although often not identified. Therefore therapy generally targets managing clinical signs including a restricted protein diet and controlling signs of hepatic encephalopathy (lactulose and antibiotic therapy). Also, antifibrotic therapy is usually administered to inhibit collagen formation and further fibrosis.

**Endocrinopathies**

The body’s endocrine organ reserve decreases with age thereby making the body less adaptive to environmental changes and stresses. Some dog develop endocrinopathies with associated clinical disease due to an underlying pathological process resulting in organ hyperfunctionality. In the geriatric dog a hyperfunctional endocrine organ is most often associated with a benign or malignant neoplasm. The diagnosis of most endocrinopathies is a based on a clinical diagnosis made in association with appropriate diagnostic testing. Therefore a definitive diagnosis of a clinically relevant endocrinopathy, especially in geriatric patients, can present a diagnostic challenge. Some of the common complaints by owners in association with endocrinopathies can be altered or masked by other concurrent illnesses or medications. The two most common chronic endocrinopathies affecting geriatric dogs include hypothyroidism and hyperadrenocorticism.

**Hypothyroidism** is considered the most common age-related change to the hypothalamo-pituitary-thyroid axis. In geriatric dogs the most common underlying cause for the development of clinical hypothyroidism is either due to lymphocytic thyroiditis or idiopathic thyroid atrophy. A definitive diagnosis of hypothyroidism can be difficult in some cases based on non-specific clinical signs and the impact non-thyroid illness and medications have on the results and interpretation of functional thyroid testing. Diseases commonly associated with euthyroid sick syndrome include hyper- or hypoadrenocorticism, liver disease, kidney disease, heart failure, diabetes mellitus, chronic infections and neoplasia; all disease more likely in the geriatric patient. Additional factors that contribute to
Euthyroid sick syndrome in dogs is underlying illness severity, nutritional status, and concurrent medications (e.g., sulphonamides, diazepam, furosemide, phenobarbital, mitotane, glucocorticoids). The functional testing of choice in a dog suspected to have hypothyroidism is to quantify multiple hormone levels concurrently including total thyroxine (TT₄), free thyroxine by equilibrium dialysis (fT₄ ED), and thyroid-stimulating hormone (TSH). Therapy for a hypothyroid dog is replacement with synthetic L-thyroxine. Assessment of response to treatment includes resolution of clinical signs and normalization serum thyroid hormone concentrations.

In the dog, the hypothalamo-pituitary-adrenal axis is impacted by aging and with age the prevalence of hyperadrenocorticism (HAC) increases in dogs. Establishing a diagnosis of HAC in geriatric patients can be a challenge as many non-adrenal diseases result in clinical signs analogous to dogs with HAC. Prior to pursuing testing of the hypothalamo-pituitary-adrenal axis, a strong clinical suspicion for HAC should be initially established based on clinical signs, hematologic and serum biochemistry abnormalities, and the absence of concurrent non-adrenal illness. The predictive value for HAC in dogs that tests positive for HAC using available screening tests (urine cortisol: creatinine ratio, ACTH stimulation test, low-dose dexamethasone test) increases proportionately with the number and severity of clinical signs and biochemical abnormalities that are consistent with HAC. Once the diagnosis of HAC is established differentiating between pituitary based diseases versus adrenal tumor is important to determine if medical (mitotane or trilostane) or surgical management is recommended.

**Cardiovascular Disease**

Age-related cardiovascular changes associated with the aging include loss of functional reserve and adaptability. Age-related changes in the canine cardiovascular system in the absence of overt heart disease include decreased blood flow, decreased arterial compliance, decreased responsiveness to beta-adrenergic stimulation and increased ventricular stiffness. Diseases of the heart of increased prevalence in geriatric dogs include valvular endocardiosis, dilated cardiomyopathy (DCM), neoplasia, and sick sinus syndrome.

Valvular endocardiosis is a chronic degenerative change that most commonly affects the mitral valve. Over time the compensatory response to valvular insufficiency includes peripheral arterial vasoconstriction and increased preload which can lead to clinical disease. Clinical signs include coughing, exercise intolerance, dyspnea, and syncope associated with left main stem bronchus compression, supraventricular arrhythmias, and the development of pulmonary edema. To definitively diagnosis endocardiosis imaging (chest radiographs and echocardiogram) and ECG are necessary. In cases with clinical disease therapeutics focus on reducing preload and afterload and include diuretics, vasodilators, and antiarrhythmics if indicated.

Breeds at increased risk for the development of DCM are Doberman pinschers, Boxers, and Cocker spaniels. Dilated cardiomyopathy is characterized by the functional loss of the myocardial pump and progressive ventricular dilation. DCM in Doberman pinschers and Boxers may be associated with ventricular arrhythmias. The diagnosis of DCM is based on imaging (chest radiographs and echocardiogram) and ECG. In dogs with clinical disease treatment is focused on supporting contractility (pimobendan), reduction in preload and afterload (ACE-inhibitors, diuretics), and control of heart rate and rhythm with antiarrhythmics.

The neoplastic diseases of the canine heart include primary versus metastatic tumors. The more common canine tumors of the heart include primary or metastatic hemangiosarcoma and heart base tumors (r/o chemodectoma, ectopic thyroid or parathyroid gland tumors). Echocardiogram is the most effect diagnostic used to rule out cardiac neoplasia and pericardial effusion which is often present at the time of diagnosis.

Sick sinus syndrome occurs in association with dysfunction of the sino-atrial node and loss of the pacemaker function of the heart. Dogs present with episodic weakness or syncope. The diagnosis is confirmed with and ECG and the treatment of choice is a pacemaker implantation.
Orthopedic Disease

Osteoarthritis (OA) is the most common degenerative orthopedic joint disease of geriatric dogs. Generally it is not a difficult chronic disease to diagnosis but can certainly impact their quality of life and be pharmacological challenge in the geriatric patient. The pharmacological interventions available for controlling the pain associated with OA can be difficult as many geriatric patients have concurrent clinical or subclinical organ dysfunctions and/or receiving multiple concurrent medications, increasing their risk for adverse drug reactions. NSAIDs are generally the drug of choice in the treatment of OA through their ability to inhibit prostaglandins, leukotrienes, proteases, and cytokines. With their beneficial effects comes the risk of adverse effects including gastrointestinal ulceration, acute kidney injury, and hepatotoxicity. Geriatric patients may be at an increased risk for NSAID associated side effects based on their loss of organ reserve and altered organ perfusion and/or the need for concurrent medications that maybe contraindicated in association with NSAIDs use. Adjunctive or alternative therapeutics to consider include tramadol, gabapentin, and anti-inflammatory and chondroprotective agents (used to slow progression of and treat chronic DJD) including the glycosaminoglycans (glycosaminoglycan polysulfate ester, pentosan polysulfate, and sodium hyaluronate). Additional alternatives include nutraceuticals (glucosamine (an oral glycosaminoglycan), chondroitin sulfate, methyl-sulfonyl-methane (MSM) and fatty acid supplementation (eicosapentaenoic acid (EPA) and docosahexaenoic acid (ω-6/ω-3: ideally < 5:1)).

References