VETERINÁRIA NOTÍCIAS

Review

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PHEOCHROMOCYTOMA IN DOGS AND CATS

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ABSTRACT

Pheochromocytoma is a functional neoplasm that produces catecholamines, located in the medullary region of the adrenal glands. As it presents nonspecific signs, scarcity of diagnostic tools and is still associated with concomitant diseases, it may not be easily considered as a differential condition among veterinarians. This is an uncommon neoplasm that usually affects dogs, with medium to advanced age and without racial predilection, being very rare in cats. Clinical manifestations vary

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according to the effects of catecholamines and/or circulatory impairment due to the local invasion of the tumor into adjacent structures. In this way, systemic arterial hypertension and consequences in target organs such as the central nervous system and kidneys can be observed, in addition to ocular changes. The definitive diagnosis is given by the histopathological analysis of the excised adrenal gland. However, the increase in the serum concentration of catecholamine metabolites may contribute to the confirmation of the disease. Adrenalectomy is the therapy of choice, but if this is not feasible, α and ß adrenergic blocking drugs should be used. The prognosis varies from reserved to favorable, based on surgical success and the presence of metastases.

1. INTRODUCTION

Pheochromocytoma is a functional neoplasm that produces catecholamines, located in the medullary region of the adrenal glands (ZINI et al., 2018). For many years it was diagnosed accidentally, since it has nonspecific signs and limited diagnostic tools (GALAC; KORPERSHOEK, 2017; SOLER ARIAS et al., 2021).

Given the importance and need to share knowledge about this disease, this work addressed information about adrenal physiology, in addition to the physiopathogenesis , clinical signs, diagnostic methods and therapies instituted for dogs with pheochromocytomas.

2. LITERATURE REVIEW

2.1. Physiology of the adrenal glands

The adrenal glands are two organs with endocrine function, located craniomedially to the kidneys and in close contact with the aorta artery and abdominal vena cava. Its embryonic development occurs from the mesoderm and neural crest, originating in this same order, the adrenal cortex and medulla (XING et al., 2015).

The cortical region is subdivided into the glomerulosa, fasciculate, and reticular zone, from which mineralocorticoids (MC), glucocorticoids (GC) and

sex steroids are produced, respectively. The medullary layer corresponds to a quarter of the adrenals size and contains modified cells called pheochromocytes or chromaffin cells. Its function is to produce, store and release adrenaline, noradrenaline (NA) and dopamine, also known as catecholamines (MIDZAK; PAPADOPOULOS, 2016; VINSON, 2016).

All adrenal cortex hormones are synthesized from cholesterol, however, specific enzymatic reactions present in each layer determine different hormones as the final product (MIDZAK; PAPADOPOULOS, 2014).

2.2. Adrenal hormones

2.2.1. Mineralocorticoids

Under physiological conditions, hemodynamic or metabolic changes that promote renal afferent arteriole hypoperfusion, reduced sodium circulation and sympathetic nervous system response to blood pressure decrease are the main stimuli for activation of the renin-angiotensin-aldosterone system (RAAS) (GONSALEZ et al., 2018). In this context, the juxtaglomerular apparatus present in the kidneys releases renin, which follows to the liver and participates in the cleavage of angiotensinogen into angiotensin I (CHAPPEL, 2016). In the lungs this is transformed into angiotensin II by the angiotensin-converting enzyme and subsequently induces the production of aldosterone (MIDZAK; PAPADOPOULOS, 2016).

Aldosterone is the main MC synthesized in the glomerulosa zone of the adrenal. Its synthesis occurs from cholesterol, when it is converted into pregnenolone in the inner membrane of the mitochondria, and then hydroxylated into progesterone. Finally, there is synthesis of deoxycorticosterone, corticosterone and aldosterone, respectively. These hormones are produced and released into the circulation without being stored in the cell (MEINEL; GEKLE; GROSSMANN, 2014) classical aldosterone receptors are located in the renal epithelium, colon and salivary glands. When stimulated, they promote renal excretion of potassium and hydrogen (reducing their circulation to serum levels), increase in blood

pressure by reabsorption of sodium and chlorine, and increase in peripheral vascular resistance (BENTO et al., 2016).

2.2.2. Glicocorticoids

GCs are regulated by the hypothalamic-pituitary-adrenal endocrine axis. In the hypothalamus, corticotropin-releasing hormone (CRH) induces the anterior pituitary to synthesize adrenocorticotropic hormone (ACTH) and this is transported via the hematogenous route to the fasciculate zone of the adrenals, where GC synthesis occurs (BENEDITO; ROSSI; CAMARGO, 2017).

The first step includes the conversion of cholesterol to pregnenolone, then to 17-hydroxypregnenolone, 17-hydroxyprogesterone, and finally, hydrolysis and cortisol formation occurs. When their production increases, GCs act with a negative feedback effect and inhibit the synthesis of CRH and ACTH. The opposite is physiologically observed, given that in the presence of reduced levels of cortisol, this pathway is stimulated (MIDZAK; PAPADOPOULOS, 2016).

Cortisol promotes catabolism and reduces protein anabolism, in addition to increasing tissue lipolysis. As a consequence, amino acids and glycerol are available for hepatic gluconeogenesis to occur. It also decreases the rate of glucose utilization by cells, thus, GC are considered hyperglycemic hormones (BENEDITO; ROSSI; CAMARGO, 2017).

2.2.3. Catecholamines

Catecholamines are synthesized from the amino acid tyrosine, which is converted into dihydroxyphenylalanine, dopamine and finally NA. Blood perfusion occurs from the cortex to the medulla, and the increase in cortisol concentration (present in the cortical layer) induces NA methylation into adrenaline (MIDZAK; PAPADOPOULOS, 2016), in addition, stress factors such as hypoglycemia, exposure to cold or excessive heat, pain, fear and changes in blood pH can also trigger catecholamine secretion (LENDERS et al., 2014).

Both adrenaline and NA act by binding to α and ß receptors and their activation triggers different biological responses. When stimulated, α1 receptors basically promote vasoconstriction, increase in systemic blood pressure, glycogenolysis and gluconeogenesis. The α2, on the other hand, control the release of NA and act on arterial vasodilation with coronary vasoconstriction and increased platelet aggregation (ZUBER et al., 2011). The ß1 receptors promote positive inotropism and chronotropism in cardiomyocytes, increase lipolysis and thermogenesis. The ß2 participate in events related to bronchodilation, glycolysis and lipolysis to increase the metabolic rate (REUSCH, 2015).

The half-life of these hormones is close to one minute, as part is taken up by postganglionic fibers or chromaffins and the rest binds to their specific receptors. Metabolization is mainly hepatic and its products are excreted in the urine in the form of metanephrines, normetanephrine or vanillylmandelic acid. Enzymes involved in the degradation process of catecholamines include monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (MIDZAK; PAPADOPOULOS, 2016).

3. PHEOCROMOCYTOMA

3.1. Definition and epidemiology

Pheochromocytoma is a functional neuroendocrine tumor of chromaffin cells (pheochromocytes) present in the adrenal medulla that produce and secrete catecholamine (ZINI et al., 2018). Considered an uncommon neoplasm, pheochromocytoma appears in 0.01 to 0.1% of the canine population and rarely in cats. It affects animals of medium to advanced age and apparently there is no sexual or racial predisposition (REUSCH, 2015; GALAC; KORPERSHOEK, 2017).

They have a tendency to proliferate slowly and have varying sizes (from 0.5 to 10 cm in diameter). In humans, the main circulating hormone is NA, whereas in dogs and cats this pattern has not yet been well determined (REUSCH; SCHELLENBERG; WENGER, 2010). About 50% of cases are malignant and target organs for metastases include the lumen of the adjacent vena cava, liver,

lungs, regional lymph nodes, spleen, kidneys and bones (REUSCH, 2015; ZINI et al., 2018).

3.2. Clinical signs

Clinical manifestations vary due to the biological effects of catecholamines or circulatory impairment secondary to local tumor invasion into adjacent structures and can lead to circulatory collapse (GALAC, 2017). Some of the main changes are described in table 1, below.

Table 1. Main clinical manifestations of pheochromocytoma in dogs.*

Catecholaminergic Effects	
Non-specific	Dysorexia, weight loss, prostration
Cardiovascular system	Tachycardia, arrhythmias, hypoperfused mucous membranes, tachypnea
Neuromuscular System	Incoordination, tremors or muscle weakness, epileptic seizures, stroke
Urinary system	Polyuria, polydipsia
Ocular changes	Intraocular hemorrhage, retinal detachment or sudden blindness
Secundary effects	
Tumor compression	Abdominal distension, pelvic limb edema, weak femoral pulse
Metastases (CNS, marrow, lungs and liver)	Epileptic seizures, neurological deficits, paresis, ataxia, spinal hypersensitivity, signs of liver disease (emesis, icterus) or bronchopathy (dyspnea and/or cyanosis).

* Adapted from REUSH, 2015 and GALAC, 2017.

A study by Reusch (2015) revealed that of the 40 dogs diagnosed with pheochromocytoma, only 10% remained without any clinical manifestations. Systemic arterial hypertension (SAH) is usually present in more than 50% of affected dogs, however, the absence of this finding does not exclude the diagnosis (GALAC; KORPERSHOEK, 2017). Impairment of circulation by tumor compression of major vessels, such as the renal artery, may also be present (REUSCH, 2015).

SAH can promote damage to target organs, such as the central nervous system, in the presence of stroke, eye complications associated with sudden blindness due

to retinal detachment (ACIERNO, et al., 2018), structural glomerulopathies (MAK; ALLEN, 2018). 2013) and cardiovascular repercussions with cardiac remodeling, myocardial ischemia, arrhythmias or cardiogenic shock (EDMONDSON et al., 2015). Polyuria and polydipsia are associated with renal injury, but also with the action of noradrenaline, which in excess, inhibits the release of vasopressin at the baroreceptor level (BARRETT; SINGER; CLAPP, 2007).

It is also possible to notice hemostatic disorders, since affected individuals are more predisposed to thrombus formation, due to activation of coagulation in the vascular endothelium or secondary to loss of antithrombin III present in glomerulopathies (LENNON et al., 2013).

3.3. Complementary exams

Abnormalities in blood count, renal and hepatic profiles, or urinalysis are uncommon, except in the presence of comorbidities. Abdominal ultrasound is widely used in veterinary medicine, as it does not require anesthesia and allows the evaluation of the architecture and size of the adrenals, as well as delimiting any mass in the gland, when present (GREGORI et al., 2015).

It is possible to measure the plasma and urinary concentration of catecholamines and their metabolites, such as metanephrine, normetanephrine and vanillylmandelic acid (SALESOV et al., 2015). A study by Soler et al (2021) revealed the vanillylmandelic acid to urinary creatinine ratio as a potential tool in the determination of pheochromocytoma in canine patients. Alternatively, serum inhibin measurement may be requested (BRÖMEL et al., 2013). It is discouraged to perform any fine needle aspiration (FNAC) cytology, even if guided by ultrasound or abdominal tomography, as it puts the patient at risk of hemorrhage or hypertensive crisis (BERTAZZOLO et al., 2014).

To obtain the definitive diagnosis, it is necessary to carry out the histopathological evaluation associated or not with the immunohistochemistry technique (GUILMETTE; SADOW, 2019).

3.4. Treatment and prognosis

The treatment of choice is adrenalectomy, although there are hemodynamic and circulatory complications during and after surgery (ZINI et al., 2018). In the presence of SAH, the use of α-adrenergic blocking drugs such as phenoxybenzamine with an initial dose of 0.25-0.5mg/kg every 12 hours is indicated approximately 2 weeks before the surgery or in those patients in whom this procedure would not be possible (GALAC, 2017). It is worth noting that, during this period, the patient should be monitored intensively to ensure that he is not induced to a state of hypotension (REUSCH, 2015).

Alternatively, prazosin acts as a competitive and selective antagonist of α1 adrenergic receptors and can be prescribed at a dose of 0.5-2 mg/kg every 8 or 12 hours. In case of persistent and severe tachycardia, the combination of ß-adrenergics such as propranolol (0.2-1 mg/kg every 8 hours) or atenolol (0.25-1 mg/kg every 12 hours) may be necessary. (REUSCH, 2015; ACIERNO et al., 2018).

The prognosis varies from reserved to favorable, as it takes into account the presence of metastases and success of adrenalectomy (LEE et al., 2020). In a study carried out by Zini et al. (2018), it was reported that of the 24 dogs with pheochromocytoma that underwent adrenalectomy, eight died in the intraoperative or immediate postoperative period. When compared with the clinical course of pheochromocytoma in humans, more than 90% of individuals have benign conditions and tumors are usually removed without complications (CHOI et al., 2015).

4. CONCLUSION

Pheochromocytoma is a disease that is often camouflaged by other conditions such as heart disease, kidney disease and systemic arterial hypertension. Thus, individuals who present impairment of such systems and target organs should have pheochromocytoma as a differential diagnosis in the investigation of the underlying cause.

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