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Invited review

Treating canine Cushing's syndrome: Current options and future prospects

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ABSTRACT

Naturally occurring hypercortisolism, also known as Cushing's syndrome, is a common endocrine disorder in dogs that can be caused by an adenocorticotrophic hormone (ACTH)-producing pituitary adenoma (pituitary-dependent hypercortisolism, PDH; 80–85% of cases), or by an adrenocortical tumor (ACT; 15–20% of cases). To determine the optimal treatment strategy, differentiating between these two main causes is essential. Good treatment options are surgical removal of the causal tumor, i.e. hypophysectomy for PDH and adrenalectomy for an ACT, or radiotherapy in cases with PDH. Because these options are not without risks, not widely available and not suitable for every patient, pharmacotherapy is often used. In cases with PDH, the steroidogenesis inhibitor trilostane is most often used. In cases with an ACT, either trilostane or the adrenocorticolytic drug mitotane can be used. Although mostly effective, both treatments have disadvantages. This review discusses the current treatment options for canine hypercortisolism, and considers their mechanism of action, efficacy, adverse effects, and effect on survival. In addition, developments in both adrenal-targeting and pituitary-targeting drugs that have the potential to become future treatment options are discussed, as a more selective and preferably also tumor-targeted approach could have many advantages for both PDH and ACTs.

Introduction

Hypercortisolism, often referred to as Cushing's syndrome, was first described by the neurosurgeon Harvey Cushing in 1932 (Cushing, 1969), and is characterized by chronically increased circulating glucocorticoids. Hypercortisolism can be either iatrogenic, caused by glucocorticoid administration, or occur naturally, caused by excessive endogenous cortisol production (Galac et al., 2010a).

Naturally occurring hypercortisolism is a common endocrine disorder in dogs, with an incidence of 1–2 cases per 1000 dogs per year (Willeberg and Priester, 1982; O'Neill et al., 2016). In 80–85% of cases, the condition is caused by an adenocorticotrophic hormone (ACTH)-secreting pituitary adenoma (pituitary-dependent hypercortisolism; PDH). In the remaining 15–20%, it is most often caused by a cortisol-secreting adrenocortical tumor (ACT), which is classified as an adrenocortical carcinoma in the majority of cases (Labelle et al., 2004; Galac et al., 2010a). Rare causes of hypercortisolism in dogs include ectopic ACTH syndrome (Galac et al., 2005) and food-dependent hypercortisolism (Galac et al., 2008).

Diagnosis

The diagnosis of hypercortisolism should be based mainly on the dog's medical history and clinical signs. Hypercortisolism usually occurs in middle-aged to older dogs (Kooistra and Galac, 2012; O'Neill et al., 2016). The most common clinical signs include polyuria, polydipsia, polyphagia, central obesity, hepatomegaly, panting, muscle atrophy, progressive bilateral alopecia, and systemic hypertension. Other clinical signs include hyperpigmentation, calcinosis cutis and insulin-resistant diabetes mellitus (Galac et al., 2010a; Behrend et al., 2013; O'Neill et al., 2016). Additionally, the pituitary tumor or ACT can induce mass-occupying effects. In cases with a large pituitary tumor, these effects include neurological signs such as anorexia, lethargy, and altered behavior. In cases with an ACT, these effects develop secondary to metastases or invasion of the ACT into the phrenicoabdominal vein or caudal vena cava (Galac et al., 2010a; Behrend et al., 2013).

When there is clinical suspicion of hypercortisolism, the results of a complete blood count (CBC), serum biochemistry panel, urinalysis and blood pressure measurement may further support the diagnosis. Abnormalities that can be found in these tests include the presence of a stress leukogram, increased serum

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alkaline phosphatase (ALP) activity, and low urine specific gravity. None of these findings are pathognomonic, but can be supportive of hypercortisolism (Behrend et al., 2013).

Endocrine tests should be used to further confirm the suspicion of hypercortisolism. It is important to only test for hypercortisolism in dogs with a high degree of clinical suspicion to decrease the chance of false-positive results (Gilor and Graves, 2011). The recommended screening tests are the low-dose dexamethasone suppression test or the urinary corticoid:creatinine ratio (UCCR). The UCCR can also be combined with the high-dose dexamethasone suppression test (HDDST). When the hypercortisolism is suppressible (>50%) by dexamethasone the dog is diagnosed with PDH. When the hypercortisolism is non-suppressible, further differentiation requires measurement of plasma ACTH concentration and/or diagnostic imaging. A CT or MRI scan is preferred to determine the size and contour of the pituitary and adrenal glands, and in case of an ACT also to detect vascular invasion and to screen for metastases (Galac et al., 2010a; Kooistra and Galac, 2012; Behrend et al., 2013). Moreover, pituitary tumors and ACTs can coexist (Greco et al., 1999; Beatrice et al., 2018), which could be missed without complete imaging. Differentiating between the two main causes of hypercortisolism is essential when choosing the optimal treatment strategy (Behrend et al., 2013).

Comparative pathobiology

Many similarities exist between hypercortisolism in dogs and humans, including the clinical signs, diagnostics, and medical care (De Bruin et al., 2009; Kooistra et al., 2009). Consequently, new insights in human hypercortisolism can advance the understanding of and treatment for canine hypercortisolism, and vice versa. In this review we will therefore not only focus on current treatment options for canine hypercortisolism, but also on advancements in the treatment of human hypercortisolism. Additionally, we discuss promising drugs that might develop into future treatment options.

Therapy

The goals of treating canine hypercortisolism would optimally be to eliminate the source of either ACTH or autonomous cortisol excess, to achieve normocortisolism, to eliminate the clinical signs, to reduce long-term complications and mortality, and to improve the quality of life. Surgical removal of the causal tumor or radiotherapy are currently the only treatment options that have the potential to eliminate the source of either ACTH or autonomous cortisol excess. However, these options are not without risks, not widely available and not appropriate for every patient. Pharmacotherapy is a commonly used treatment that aims to eliminate the clinical signs of the condition. A combination therapy of medical treatment with radiotherapy is also possible (Galac et al., 2010a; Pérez-Alenza and Melián, 2016).

Without treatment, dogs with PDH have a median survival time of 359 days (95% confidence interval (CI), 271–829) (Kent et al., 2007) to 506 days (95% CI, 292–564) (Nagata et al., 2017). There are no data on the survival of dogs with an ACT without treatment.

Surgery

Hypophysectomy

Hypophysectomy in dogs is performed using a transsphenoidal approach where the entire pituitary gland is removed (Meij, 2001; Meij et al., 2002). In a recent study with a large cohort of 306 dogs with PDH that underwent hypophysectomy (van Rijn et al., 2016), 91% of the dogs were alive after 4 weeks, of which remission was confirmed in 92%. Of the dogs that were in remission, disease recurrence was observed in 27%. The median survival time was 781 days (range, 0–3808 days) and the median disease-free interval of the dogs that were in remission was 951 days (range, 31–3808 days).

Replacement therapy after hypophysectomy consists of lifelong administration of glucocorticoids and thyroxine, and temporary administration of desmopressin, a synthetic vasopressin analogue (Meij, 2001; Hanson et al., 2005; Galac et al., 2010a). The main complications of hypophysectomy are perioperative death, transient mild postoperative hypernatremia, transient reduction or cessation of tear production, prolonged or permanent diabetes insipidus, and recurrence of hypercortisolism (Meij, 2001; Meij et al., 2002).

Factors that negatively influence the prognosis include a high pituitary height/brain area (P/B) value, old age, high preoperative circulating ACTH concentration, and high pre- and postoperative UCCRs (Hanson et al., 2007; van Rijn et al., 2015, 2016). Although a high P/B value is a negative prognostic indicator, hypophysectomy remains a good treatment option also for large pituitary tumors (Fracassi et al., 2014; van Rijn et al., 2016). The main limitation of hypophysectomy is that it is available only in large veterinary centers with an established team of experienced surgeon(s), anesthetist(s), critical care specialist(s) and endocrinologist(s), with consequently high initial costs (Pérez-Alenza and Melián, 2016).

Adrenalectomy

Adrenalectomy is recommended for dogs with uni- or bilateral ACT. Adrenalectomies were traditionally performed as ventral or paracostal open laparotomies. Perioperative mortality rates were quite high in initial studies (Scavelli et al., 1986), but improved in later studies (van Sluijs et al., 1995; Anderson et al., 2001; Kyles et al., 2003; Schwartz et al., 2008; Massari et al., 2011) and are as low as 6–8% in most recent studies (Lang et al., 2011; Mayhew et al., 2014). Adrenalectomy can also be performed laparoscopically. Laparoscopic adrenalectomy has been used in human medicine since the early 1990s and has recently been gaining interest and shown to have benefits in veterinary medicine as well (Naan et al., 2013; Mayhew et al., 2014).

Reported median survival times for dogs undergoing adrenalectomy range from 778 days (range, 1–1593) (Anderson et al., 2001) to 953 days (range, 0–1941) (Massari et al., 2011). When dogs survive the perioperative period, the long-term survival is good (Anderson et al., 2001; Lang et al., 2011). The main complications that can occur include minor to severe hemorrhage, hypotension, tachycardia and peri-operative death (van Sluijs et al., 1995; Lang et al., 2011; Massari et al., 2011; Mayhew et al., 2014). The tumor capsule can rupture, possibly more often in laparoscopic than in open adrenalectomies, but does not commonly lead to tumor regrowth (Mayhew et al., 2014). The main complications that can occur postoperatively include pancreatitis and thromboembolism (van Sluijs et al., 1995; Anderson et al., 2001; Mayhew et al., 2014). The reported hypercortisolism recurrence rate varies between 12% (Anderson et al., 2001) and 30% (van Sluijs et al., 1995), which can be either because of regrowth of the ACT or metastases.

Adrenalectomy is not recommended in patients that have metastases or extensive vascular invasion, which is why thorough presurgical diagnostic imaging is imperative. Vascular invasion does not necessarily exclude patients from undergoing adrenalectomy, since some studies indicate that tumor invasion in the caudal vena cava does not affect perioperative mortality (Kyles et al., 2003; Lang et al., 2011), and techniques to remove the tumor thrombus have improved (Mayhew et al., 2018). However, when the vascular invasion is extensive, in particular when the tumor invasion in the vena cava extends beyond the hepatic hilus, the perioperative mortality rates can increase (Barrera et al., 2013).