Canine Hypercortisolism (Cushing's Syndrome): **Treatment**

Introduction

- Spontaneous hypercortisolism is one of the most common endocrine disorders of middle-aged and elderly dogs, with an estimated incidence of 1 per 1000 dogs per year. In about 85% of cases it is due to a pituitary (micro- or macro-) adenoma that hypersecretes ACTH. In about 15% of cases it is due to an adenoma or (more often) carcinoma of the adrenal cortex that autonomously hypersecretes cortisol.

- The diagnosis of hypercortisolism should be based on the medical history, clinical signs, biochemical changes and endocrine tests (e.g. low-dose dexamethasone suppression test).

- Although imaging is very important in dogs with hypercortisolism, hypercortisolism cannot be diagnosed solely with imaging.

- In addition to the biochemical effects of cortisol excess, clinical signs may develop secondary to mass-occupying effects of a pituitary or adrenocortical tumour.

- It is important to differentiate pituitary-dependent hypercortisolism and hypercortisolism due to an adrenocortical tumour because treatment and prognosis differ.

- The presence of an adrenal tumour can be determined by abdominal ultrasonography. Moreover, ultrasonography can be used to estimate the size of the adrenal tumour, and to identify possible vascular or local soft tissue invasion, metastases (for example in the liver) and contralateral adrenocortical atrophy.

- Pituitary imaging (by contrast-enhanced CT or MRI) provides valuable information regarding treatment options and prognosis. Pituitary macrotumours may result in headache (or neurological signs), therefore pituitary imaging is recommended in all dogs at the time of diagnosis of pituitary-dependent hypercortisolism.

- An adrenal tumour and pituitary tumour may occur simultaneously. Consequently, visualization of both the pituitary area and the adrenals is recommended in dogs with hypercortisolism.

- The goal of treating canine hypercortisolism would optimally be to eliminate the source of either ACTH excess or autonomous cortisol excess, to achieve normocortisolism, to eliminate clinical signs, to reduce long-term complications and mortality, and to improve the quality of life and life expectancy.

- Surgical removal of the causal tumour or radiotherapy are currently the only treatment options that have the potential to eliminate the source of either ACTH excess 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 hypercortisolism.

- Without treatment, dogs with pituitary-dependent hypercortisolism have a median survival time of about 1 year.

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Surgery: hypophysectomy

- Remission rate after transsphenoidal hypophysectomy is > 90%.
- The median survival rate after hypophysectomy is > 2 years.
- The median disease-free interval after hypophysectomy is > 2.5 years; in about 40% of dogs hypercortisolism recurs within 4 years.
- Although a large pituitary tumour is a negative prognostic indicator, hypophysectomy remains a good treatment option for large pituitary tumours.
- Replacement therapy after hypophysectomy consists of lifelong administration of glucocorticoids and thyroxine, and (temporary) administration of desmopressin.
- Permanent diabetes insipidus and transient reduction or cessation of tear production are common complications of hypophysectomy.

Surgery: adrenalectomy

- Adrenalectomy (ventral or paracostal open laparotomy or laparoscopically) is recommended for dogs with uni- or bilateral adrenocortical tumours causing hypercortisolism.
- The median survival rate after adrenalectomy is > 2 years.
- When dogs survive the perioperative period, the long-time survival is very good.
- The reported recurrence rate varies between 12% and 30%, which can be either because of regrowth of adrenocortical tumour tissue or metastases.
- Vascular invasion does not necessarily exclude dogs from undergoing adrenalectomy.
- After adrenalectomy dogs have to be treated temporarily (about 6 weeks) with glucocorticoids (in a tapering dosage).

Radiotherapy

- Radiotherapy can be useful in decreasing tumour size and reducing neurological signs in cases of large pituitary tumours.
- Usually, radiotherapy is performed in 12 fractions, which requires the dog to be under anaesthesia on 12 occasions; a single-session, focused stereotactic radiosurgery using a Gamma Knife may be a promising alternative.
- Reduction of clinical signs of hypercortisolism can vary considerably between patients; temporary or permanent additional pharmacotherapy may, therefore, be required to manage hypercortisolism.
- The reported median survival time varies between 1.5 and 2 years.

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Pharmacotherapy: trilostane

- Trilostane competitively inhibits the steroidogenic enzyme 3-beta-hydroxysteroid dehydrogenase, which is required for the production of all classes of adrenocortical hormones. Trilostane therefore inhibits both cortisol production (resulting in a compensatory increase in plasma ACTH concentration) and aldosterone production.

- Being an enzyme inhibitor, trilostane does not directly affect the growth of the tumour.

- Because food increases the rate and extent of absorption of trilostane, trilostane should always be given with food (also on the days blood samples are taken for the monitoring of the trilostane dosage).

- The datasheet for trilostane states a trilostane starting dose of approximately 2 mg/kg given once daily, but the authors routinely start at 0.5 mg/kg twice daily in case of pituitary-dependent hypercortisolism and 0.25 mg/kg twice daily in case of an adrenal tumour causing hypercortisolism with the owner's consent to use an off-label dose. Regardless of size of the dog, it is the authors' advise not to start with a dose higher than 30 mg BID.

- An adequate dose of trilostane can increase the dog's activity and reduce polyuria, polydipsia and polyphagia within 1-2 weeks. More time is needed to observe notable improvements in the skin and hair coat, which can take months. The hair coat can sometimes initially appear to worsen.

- Trilostane is usually well tolerated. The main adverse effects arise from transient hypocortisolism (sometimes combined with hypoaldosteronism). In most dogs, the adverse effects resolve once trilostane treatment is withdrawn. In such cases, continuation of treatment with a lower dose is recommended when clinical signs of hypercortisolism recur. However, in some dogs, the hypoadrenocorticism can be permanent; which is possibly the result of adrenocortical necrosis, and can be fatal in severe cases.

- The median survival times of dogs with pituitary-dependent hypercortisolism treated with trilostane range from 2 to 3 years. The median survival time of dogs with hypercortisolism due to an adrenal tumour is around 1 year.

- Frequent monitoring is essential for the successful management of hypercortisolism with trilostane. In all methods, evaluation of the clinical signs is the first and most important step.

- The ACTH stimulation test can be used to monitor the adrenal cortex' reserve capacity, especially to prevent hypocortisolism. Although the datasheet for trilostane states that the ACTH stimulation test should be performed 4-6 hours after trilostane administration, the authors recommend to perform the ACTH stimulation at 2-3 hours after trilostane administration.

- An alternative method to monitor trilostane treatment is to measure the pre-pill cortisol concentration. It is less expensive than the ACTH stimulation test and does not require the availability of synthetic ACTH, however it mainly reflects basal (pulsatile) cortisol secretion and is highly influenced by stress. Moreover, it is not a measure of adrenocortical reserve and will, therefore, not reflect the safety of trilostane therapy.

- Dogs with hypercortisolism treated with trilostane are checked every 2-3 weeks until clinical signs of hypercortisolism are under control and no adverse effects are present. If clinical signs indicate that the trilostane dose needs to be increased, endocrine testing will help to determine whether the dose has to be increased or the frequency of administration has to be increased: if the ACTH stimulation test shows good adrenocortical reserve capacity the dose is increased; if the ACTH stimulation test shows limited adrenocortical reserve capacity the frequency of administration may be increased.

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Pharmacotherapy: mitotane (o,p'-DDD)

- Mitotane (o,p'-DDD) is an adrenocorticolytic drug that leads to progressive necrosis of adrenocortical cells (including metastases).
- The use of mitotane for the treatment of hypercortisolism has largely been replaced by that of trilostane because trilostane is usually as effective, is safer to handle, and has been associated with fewer adverse effects than mitotane.
- Mitotane is a good therapeutic option for those cases (about 10-15%) that respond poorly to trilostane.
- In case of an adrenocortical tumour that can not be treated surgically (for example because the tumour has metastasized), treatment with mitotane is an option because it has the added advantage that it can destroy adrenocortical cells.
- For treatment with mitotane the dog can best be referred to an endocrinologist.

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