

Review

# Progress in transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in dogs and cats

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## Abstract

Cushing's disease or pituitary-dependent hyperadrenocorticism (PDH) is common in dogs and rare in cats. PDH is caused by a pituitary tumor producing adrenocorticotropin (ACTH). Pituitary imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is required to assess the size and location of the pituitary adenoma in relation to the surgical landmarks. In a specialized veterinary institution, microsurgical transsphenoidal hypophysectomy has proven to be a safe and effective treatment for dogs ( $n = 84$ ) and cats ( $n = 7$ ) with Cushing's disease. Pituitary surgery requires a team approach and the neurosurgeon performing hypophysectomies must master a learning curve. The surgical results compared favorably with those for dogs with PDH treated medically with mitotane at the same institution. The recurrence rate after initially successful surgery increases with longer follow-up times. Pituitary function testing in 39 dogs with PDH treated with hypophysectomy revealed that, much more so than the other adenohypophyseal cell types, residual corticotropes present in the sella turcica after surgery are functional. Such normal ACTH secreting cells may maintain normocorticism whereas residual adenoma cells may lead to mild recurrence after relatively long periods of remission. Microsurgical transsphenoidal hypophysectomy is an effective treatment for canine and feline Cushing's disease.

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## 1. Introduction

Transsphenoidal selective adenectomy is the primary therapy for Cushing's disease in humans (Melby, 1988). In dogs the most common method of treatment for Cushing's disease or pituitary-dependent hyperadrenocorticism (PDH) is medical treatment with mitotane, which causes selective destruction of the adrenal cortex (Rijnberk and Belshaw, 1988; Kintzer and Peterson, 1991). In cats the most common treatment is bilateral adrenalectomy (Duesberg et al., 1995b). In dogs and cats the adrenocorticotropin (ACTH) cell adenoma may originate from the pars distalis or the pars intermedia of the adenohypophysis. A less common indication for pituitary surgery in cats is a growth hormone (GH)-secreting cell adenoma causing acromegaly, and in dogs

an endocrinologically non-functional macroadenoma that produces symptoms due to a pituitary mass effect. Ideally, the treatment of canine and feline PDH should be directed at eliminating the pituitary lesion causing excessive ACTH secretion. Early diagnosis of PDH, pituitary imaging, and treatment at the pituitary level should be the hallmarks of a successful treatment protocol.

Studies of hypophysectomy by medical investigators and neurosurgeons led Markowitz and Archibald (1956) to describe experimental transsphenoidal hypophysectomy in dogs (Markowitz and Archibald, 1956; Markowitz et al., 1964). Transsphenoidal hypophysectomy was introduced in veterinary clinical practice at the end of the 1960s and preliminary results in four dogs with Cushing's syndrome were reported as encouraging (Rijnberk et al., 1968, 1969). Few clinical reports have been published since then. In the last three decades, the surgical technique of transsphenoidal hypophysectomy in dogs has been modified (Lubberink and Rijnberk,

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1974; Niebauer and Evans, 1988; Meij et al., 1997c), and the introduction of advanced pituitary imaging techniques has improved tumor localization (Voorhout et al., 1988; Duesberg et al., 1995a; Kooistra et al., 1997; Meij et al., 1998). As the likelihood of a favorable outcome of pituitary surgery has improved, this surgical approach has become the treatment of choice for canine (Meij et al., 1998) and feline (Meij et al., 2001) PDH in our institution.

## 2. Pituitary imaging

Computed tomography (CT) of the pituitary gland in dogs and cats with PDH is a surgical prerequisite for assessment of pituitary size and for localization of the gland in relation to surgical landmarks (Meij et al., 1998, 2001). By viewing sequential CT images, the position of the center of the pituitary gland can be correlated with the position of the dorsum sellae and the hamular processes, and to the shape of the outer lamina of the sphenoid bone. CT enables direct visualization of the pituitary gland and has been used for imaging the normal pituitary gland (Voorhout, 1990; Meij et al., 1997c) and pituitary tumors in dogs (Voorhout et al., 1988; Kooistra et al., 1997; Meij et al., 1998). Because the pituitary gland lies outside the blood-brain barrier, radiographic contrast medium diffuses freely from the vascular space to the interstitial space. In healthy dogs, the pituitary gland is 6–10 mm in length, 5–9 mm in width, and 4–6 mm in height (Voorhout, 1990). Enlarged and non-enlarged glands can be identified by means of the ratio between the height of the pituitary gland and the area of the brain (P/B ratio), measured on a CT image through the center of the pituitary: enlarged glands have a P/B ratio greater than 0.31 and non-enlarged glands have a ratio less than 0.31 (Kooistra et al., 1997). Macroadenomas of the pituitary gland are easily detected on contrast-enhanced CT images because of their altered size and shape. The appearance of an enlarged pituitary gland in a dog with PDH before and after hypophysectomy is illustrated in Fig. 1. However, a normal pituitary appearance does not exclude the presence of microadenomas, because these may not change the size or shape of the pituitary. Classification of pituitary adenomas according to the standards of human medicine into microadenomas ( $\leq 10$  mm) and macroadenomas ( $> 10$  mm) is not useful in veterinary medicine because pituitary adenomas in the dog that are between 6 and 10 mm in height enlarge the gland and therefore cannot be classified as microadenomas.

Direct visualization of the pituitary adenoma is only possible when the imaging characteristics of the adenoma are different from those of the surrounding normal pituitary tissue (Meij, 1999). The enhancement pattern of the neurohypophysis during dynamic contrast

enhanced CT has been called the ‘pituitary flush’. The displacement, distortion, or disappearance of the pituitary ‘flush sign’ in the early phase of dynamic CT examinations can be used to identify (micro)adenomas in dogs (Van der Vlugt et al., 1996).

## 3. Surgical technique

Pituitary surgical techniques include selective removal of the pituitary adenoma (adenomectomy), removal of the adenohipophysis (adenohypophysectomy), removal of a significant part of pituitary tumor mass in the case of a macroadenoma (pituitary debulking), or complete removal of the pituitary gland (hypophysectomy).

Hypophysectomy in dogs and cats is performed by a transsphenoidal approach under general inhalation anesthesia (Meij et al., 1997c). Following electrosurgical incision of the palatine mucosa and the mucoperiosteum, the exact position of the burr slot is determined by correlating the location of the pituitary fossa and pituitary gland with that of the pterygoid hamular processes and the shape of the outer cortical lamina on sequential, contrast-enhanced CT images. Access to the pituitary fossa is obtained with an air-powered burr. When the pituitary gland becomes visible through the paper-thin inner cortical layer, burring is discontinued and a  $3.3\times$  operating loupe is used to provide magnification. Bone punches are used to enlarge the opening created in the inner cortical lamina of the sphenoid bone (Fig. 2). The dura mater is incised in a cruciate pattern and the pituitary protrudes through the resulting opening. The pituitary adenoma is detached from the fossa circumferentially using a small ball-tipped hook and is extracted through the dural opening using fine neurosurgical grasping forceps. The hypophyseal fossa is inspected for completeness of hypophysectomy by the following criteria: (1) unobstructed view of the ventral hypothalamic surface and the opening to the third ventricle, and (2) absence of pituitary remnants upon careful exploration of the hypophyseal fossa and the dorsum sellae. The wound is closed by filling the pituitary fossa with absorbable gelatine sponge, filling the burr slot in the sphenoid bone with bone wax, and suturing the soft palate in two separate layers.

Postoperative care in the intensive care unit includes close monitoring of vital functions, plasma electrolytes (sodium and potassium), plasma osmolality, and central venous pressure. These parameters guide the administration of IV fluids; however, spontaneous oral water intake is encouraged as soon as the patient is awake. Postoperative medication includes antibiotics and analgesics. Hormone replacement is started immediately and consists of hydrocortisone (1 mg/kg for every 6 h) and desmopressin, a vasopressin analogue (4  $\mu$ g administered as a drop into the conjunctival sac every 8 h). As

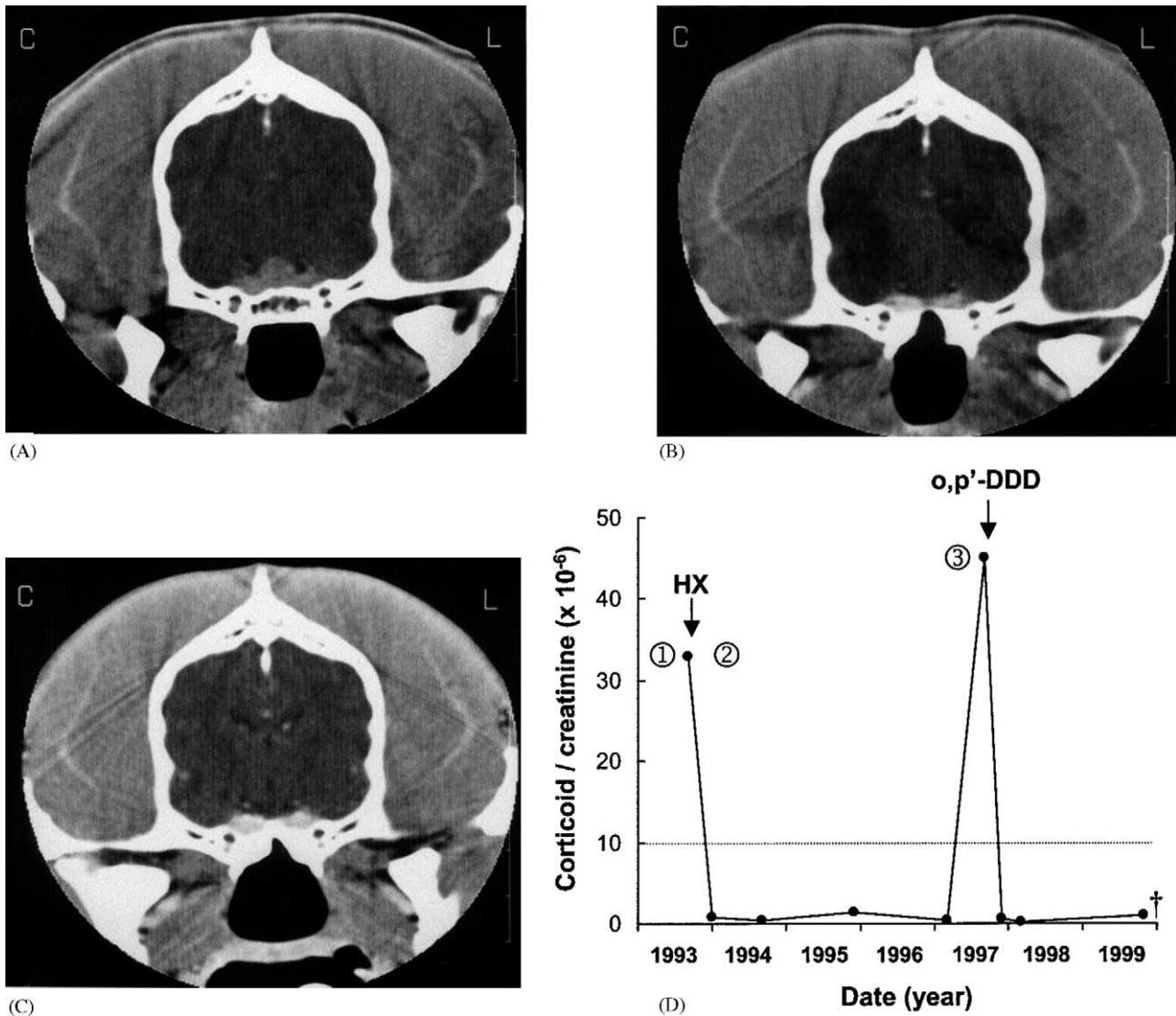


Fig. 1. Contrast-enhanced transverse CT images through the pituitary fossa before (A, 1) and 3 months after (B, 2) transsphenoidal hypophysectomy (HX) in a 10-year-old female Bouvier dog with pituitary-dependent hyperadrenocorticism (PDH). The pituitary was enlarged (pituitary height/brain area ratio = 0.45, normal < 0.31) and measured 7.3 mm in height and 8.3 mm in width (A). The urinary cortisol/creatinine (C/C) ratio decreased from  $33 \times 10^{-6}$  (normal <  $10 \times 10^{-6}$ ) before surgery to  $< 1.0 \times 10^{-6}$  after surgery (D). Contrast-enhanced CT images at 3 months after surgery showed no residual pituitary tissue (B). The urinary C/C ratios fluctuated around  $1 \times 10^{-6}$  for the following 4 years (D). At the age of 14 years, 4 years after hypophysectomy, hyperadrenocorticism recurred and the urinary C/C ratio rose to  $45 \times 10^{-6}$  (D). Endocrine function tests revealed PDH and contrast-enhanced CT images at the time of recurrence showed bony closure of the sphenoid slot and no visible regrowth of a pituitary adenoma mass (C, 3). The dog was treated with mitotane (o,p'-DDD) and signs of hyperadrenocorticism went in remission (D). The dog eventually passed away spontaneously at the age of 15 years (†).

soon as the dog has resumed eating and drinking, oral replacement therapy is started: cortisone acetate (1 mg/kg every 12 h) and thyroxine (15 µg/kg every 12 h). Over a period of 4 weeks the dose of cortisone acetate is gradually tapered to 0.25 mg/kg every 12 h. Desmopressin (0.01%) is administered for 2 weeks, 1 drop into the conjunctival sac every 8 h.

Endocrine functions (urinary corticoid/creatinine ratios and plasma thyroxine) are monitored after hypophysectomy, preferably every 4–6 months.

#### 4. Results and pitfalls

The median age of the dogs at the time of pituitary surgery was 10 years. Six of 84 dogs with PDH that were treated by transsphenoidal hypophysectomy died within 4 weeks of surgery and were considered procedure-related mortalities. In another 6 dogs the tumor was removed incompletely, as was apparent from elevated corticoid/creatinine ratios in urine samples at 8 weeks after surgery. The latter cases were considered incom-

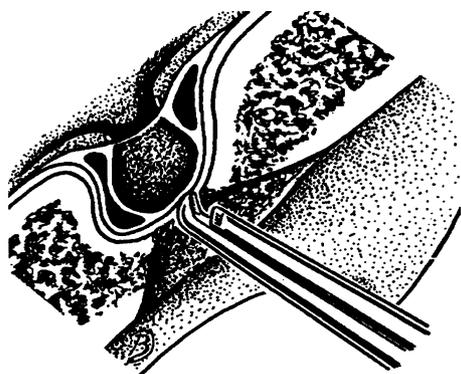


Fig. 2. Transsphenoidal approach to the canine pituitary gland.

plete hypophysectomies and residual pituitary tumor tissue was confirmed by CT. Therefore, the overall response rate was 86%, i.e. 72 of 84 dogs went into remission after surgery.

Survival and the proportion of disease-free dogs were calculated for the group of 84 dogs with Cushing's disease that underwent transsphenoidal hypophysectomy and included 52 dogs of a previous study (Meij et al., 1998). The estimated survival rate after transsphenoidal hypophysectomy was 84% (95% confidence interval (CI): 74–91%) at 1 year, 82% (95% CI: 71–89%) at 2 years, and 79% (95% CI: 65–87%) at 3 years (Fig. 3). The proportion of disease-free dogs was 91% (95% CI: 79–96%) at 1 year and 80% (95% CI: 65–90%) at 2 years (Fig. 4).

There is a learning curve for developing expertise in doing transsphenoidal hypophysectomy and dealing with the initial complications. Comparison of the results of hypophysectomy cases 1–26 and 27–52 (Meij et al., 1998) revealed a lower mortality (i.e. mortality within 4

weeks after surgery irrespective of the cause of death) in the second group. In the present study, five dogs in the first series (1–42) died within 4 weeks of surgery whereas in the second series (43–84) only one dog died within 4 weeks of surgery. The better results were attributed to improved knowledge of the surgical procedure and to improved postoperative care. Causes of death were severe postoperative hyponatremia, severe postoperative hypernatremia, cerebral edema, bronchopneumonia, ketoacidosis, and renal failure.

The main peri-operative and long-term complications in dogs were transient, mild, postoperative hypernatremia (most cases); transient reduction or cessation of tear production due to neuropraxia of the lacrimal gland innervation (25%); prolonged (20%) or permanent (10%) diabetes insipidus due to decreased availability of vasopressin; and secondary hypothyroidism due to insufficient substitution with thyroxine. Elevated plasma sodium levels (150–160 nmol/l) usually normalize when oral water intake resumes. In the case of keratoconjunctivitis sicca, normal tear production resumed after a median of 10 weeks. In dogs with prolonged diabetes insipidus, desmopressin was stopped after a median of 4 months, and in dogs with permanent diabetes lifelong treatment with 1 or 2 drops of desmopressin was required.

## 5. Pituitary and adrenocortical function after transsphenoidal hypophysectomy in dogs

After removal of the pituitary gland containing the adenoma, the levels of pituitary hormones decrease sharply and approach the lower limit of the hormone

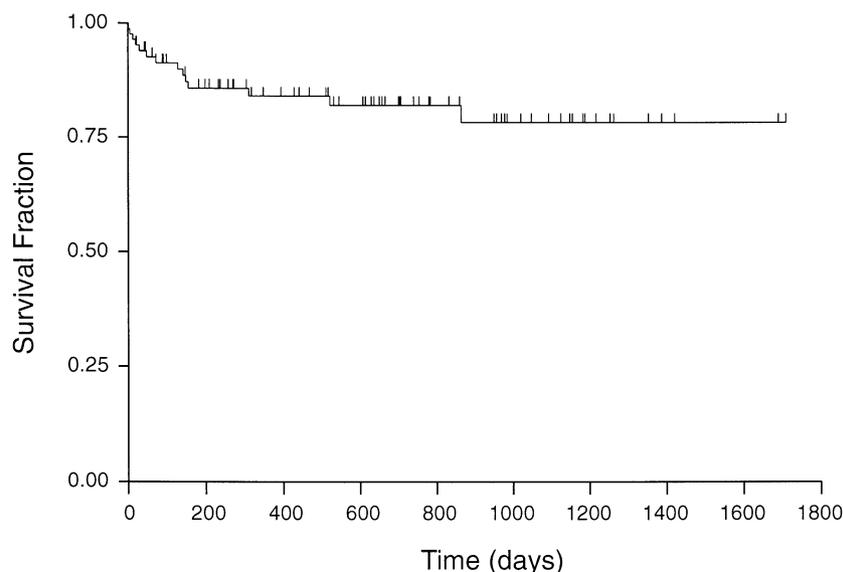


Fig. 3. Survival curve after transsphenoidal hypophysectomy for 84 dogs with pituitary-dependent hyperadrenocorticism. Censored cases, i.e. dogs that died from unrelated causes or which were still alive at the time of follow-up, are represented by vertical bars.

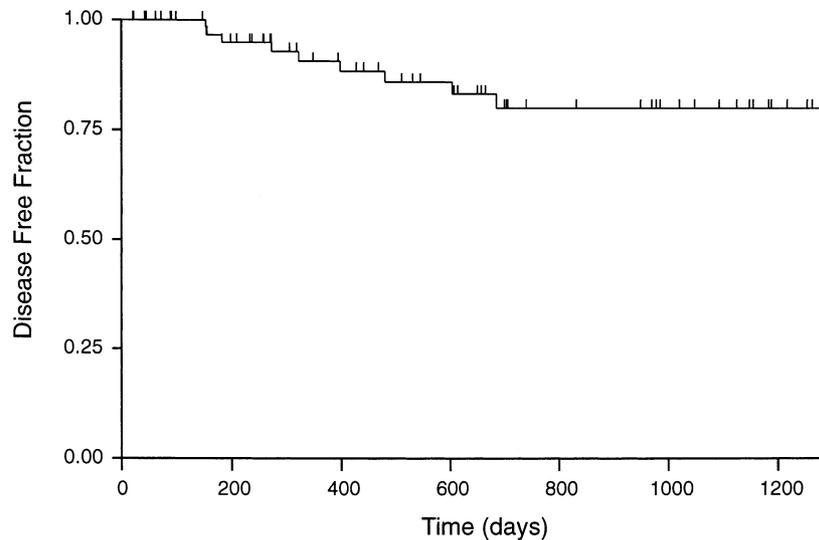


Fig. 4. Disease-free interval curve after transsphenoidal hypophysectomy for 72 dogs with pituitary-dependent hyperadrenocorticism. Disease-free is defined as remission of signs of hyperadrenocorticism and basal urinary corticoid/creatinine ratios  $< 10 \times 10^{-6}$ .

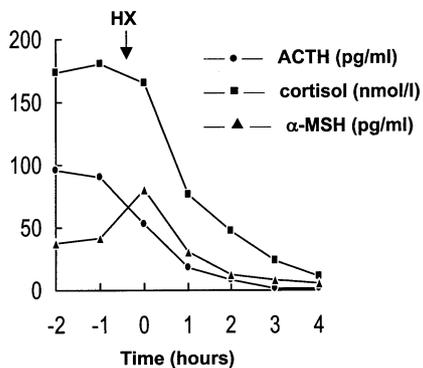


Fig. 5. Plasma adrenocorticotropic (ACTH), cortisol, and  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH) concentrations before and immediately after transsphenoidal hypophysectomy (HX) in a 7-year-old female Shar-Pei with pituitary-dependent hyperadrenocorticism. The urinary cortisol/creatinine (C/C) ratio before surgery was  $80 \times 10^{-6}$  (normal  $< 10 \times 10^{-6}$ ) and CT images revealed a slightly enlarged pituitary (pituitary height/brain area ratio = 0.36, normal  $< 0.31$ ) with a height of 5.3 mm. Following removal of the pituitary gland including the adenoma, hormone levels typically decreased to the lower limit of the reference range over 4 h. Clinical signs of hyperadrenocorticism remitted and urinary C/C ratios at 2 and 8 weeks after surgery were  $0.4 \times 10^{-6}$  and  $< 1 \times 10^{-6}$ .

assay (Fig. 5). In a group of 39 dogs with PDH that underwent transsphenoidal hypophysectomy, pituitary function was investigated using combined administration of four hypothalamic releasing hormones (Meij et al., 1997a). At 8 weeks after surgery there were no plasma GH, luteinizing hormone (LH), prolactin (PRL), and thyroid-stimulating hormone (TSH) responses to stimulation, whereas plasma ACTH and cortisol responses were small but significant (Fig. 6). Four of 39 dogs had residual pituitary tissue and 35 of 39 dogs developed clinical remission of hyperadrenocorticism and their urinary corticoid/creatinine ratios became

normal. Three of the 35 dogs showed a recurrence after initial remission. After hypophysectomy, 6 of 35 dogs had an increase in plasma ACTH  $< 10$  ng/l in response to corticotropin-releasing hormone (CRH) and 29 of 35 dogs had an increase in plasma ACTH  $> 10$  ng/l. All 3 dogs that developed a recurrence had a plasma ACTH response  $> 10$  ng/l to CRH during the period of initial remission after surgery (Meij et al., 1997a). It was concluded that, of the adenohypophyseal cells present in the sella turcica after hypophysectomy, corticotropes may show residual function. Much more so than the other cell types, normal corticotropes tend to remain functional and may even maintain normocorticism. Residual ACTH adenoma cells may lead to mild hyperadrenocorticism after relatively long periods of remission.

Hyperadrenocorticism recurred in 11 of 72 dogs (15.3%) at 5–47 months after surgery. In the 72 operated dogs, the median urinary cortisol/creatinine (C/C) ratio (normal  $< 10 \times 10^{-6}$ ) decreased from  $46.8 \times 10^{-6}$  (range  $10.6$ – $502.5 \times 10^{-6}$ ) prior to surgery to  $2 \times 10^{-6}$  (range  $0.1$ – $9.5 \times 10^{-6}$ ) at 2 months after hypophysectomy. These C/C ratios were measured in urine samples collected at home 24 h after cortisone medication. The range in urinary C/C ratios after surgery suggests that these dogs had residual adrenocortical function after removal of most of the pituitary gland including the adenoma. Some dogs had urinary C/C ratios at the lower limit of the assay ( $0.2 \times 10^{-6}$ ) (Fig. 7A), indicating the absence of adrenocortical function and strict dependence on cortisone replacement. In other dogs, urinary C/C ratios fluctuated in the normal reference range ( $< 10 \times 10^{-6}$ ), indicating a state of normocorticism. Indeed, in these dogs cortisone administration could be stopped (Fig. 7B). However, normocorticism could also be seen as a prelude to recurrent

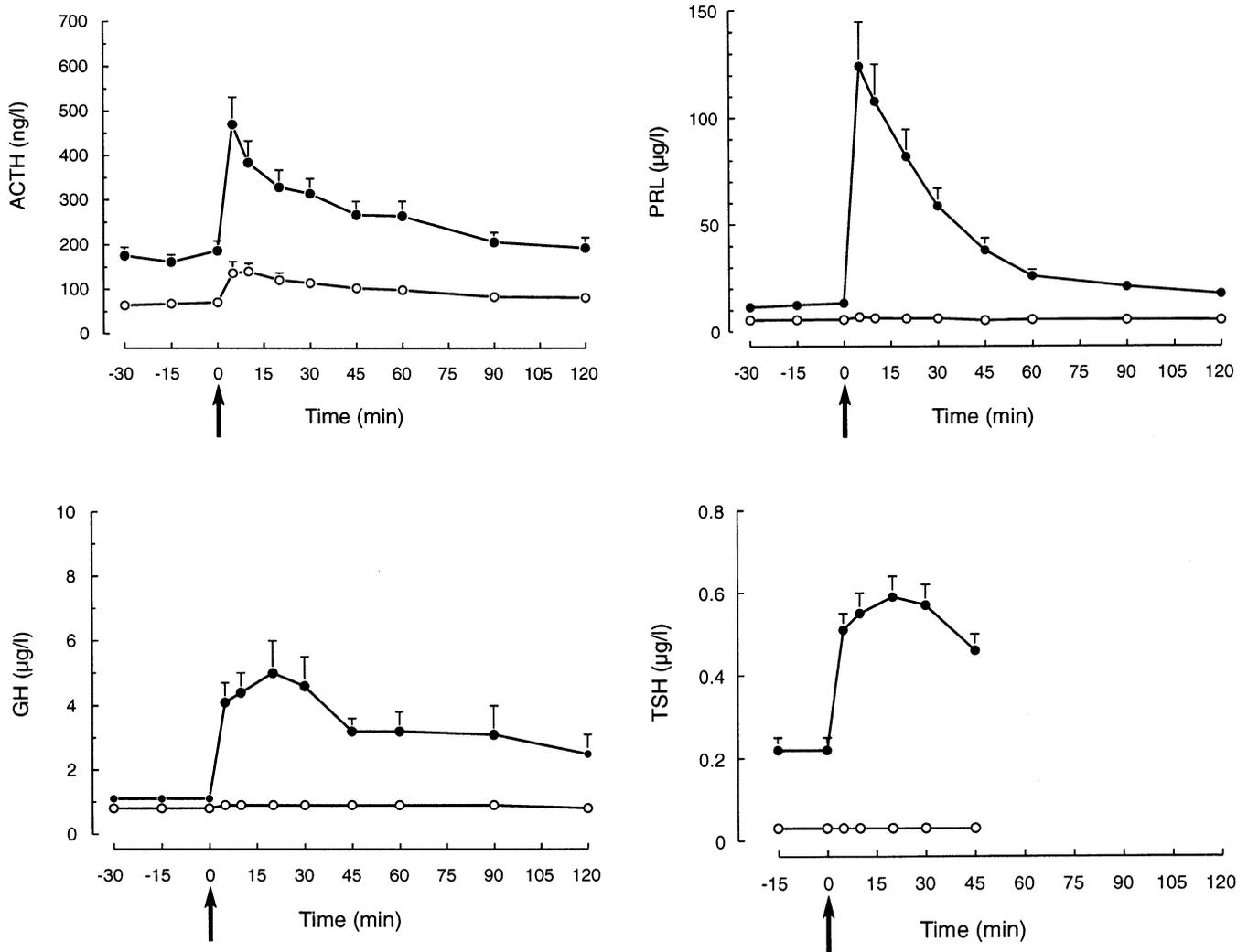


Fig. 6. Plasma adrenocorticotropin (ACTH), growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH) responses (mean  $\pm$  SEM) in 39 dogs with pituitary dependent hyperadrenocorticism after the rapid sequential IV injection (arrow) of four hypothalamic releasing hormones (4RH), before ( $\bullet$ ) and at 8 weeks after ( $\circ$ ) transsphenoidal hypophysectomy, in the following order and doses: 1  $\mu$ g of corticotropin-releasing hormone (CRH)/kg, 1  $\mu$ g of GH-releasing hormone (GHRH)/kg, 10  $\mu$ g of gonadotropin-releasing hormone (GnRH)/kg, and 10  $\mu$ g of thyrotropin-releasing hormone (TRH)/kg.

mild hyperadrenocorticism, and in dogs that lived sufficiently long after pituitary surgery this may have led to a full recurrence (Fig. 7B). Recurrence is thought most likely to be caused by regrowth of adenoma cells left in situ. After transsphenoidal hypophysectomy in healthy dogs, the sella turcica was usually found to contain microscopic nests of pituitary cells (Meij et al., 1997b).

The results of hypophysectomy as treatment for canine Cushing's disease compare favorably with those for mitotane treatment in the same institution (Den Hertog et al., 1999). Transsphenoidal hypophysectomy in dogs with Cushing's disease renders a similar short-term (1 year follow-up) survival rate as treatment with mitotane, whereas the recurrence rate in this period is

lower for the surgical procedure. Also, adverse effects such as the development of Addison's disease and neurological signs due to an expanding pituitary tumor complicate mitotane treatment. These complications do not arise after pituitary surgery. This may explain the lower 2-year (69%) and 3-year (61%) survival rates after mitotane treatment (Den Hertog et al., 1999) compared with the 2-year (82%) and 3-year (79%) survival rates after transsphenoidal hypophysectomy (this study). In two dogs that developed a recurrence 4 years after surgery, there was no apparent regrowth of the pituitary mass on contrast-enhanced CT images (Fig. 1C). Given that surgical skills improve and procedure-related mortality decreases, it is to be expected that the survival rate will improve with time.

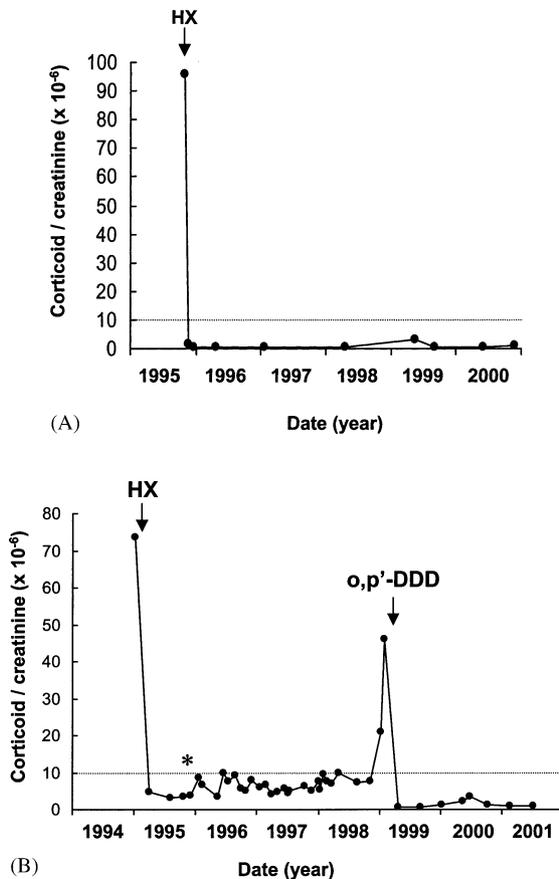


Fig. 7. Urinary corticoid/creatinine (C/C) ratios in 2 dogs with pituitary-dependent hyperadrenocorticism (PDH) that underwent transsphenoidal hypophysectomy (HX). (A) In a 8-year-old female Dachshund (pituitary height = 3.5 mm; pituitary height/brain area ratio (P/B) = 0.21, normal < 0.31), the urinary C/C ratio decreased from  $96 \times 10^{-6}$  (normal <  $10 \times 10^{-6}$ ) to near zero levels, necessitating lifelong cortisone replacement. (B) In a 10-year-old male Yorkshire terrier (pituitary height = 2.9 mm; P/B = 0.21) the urinary C/C ratio decreased from  $74 \times 10^{-6}$  before surgery to levels fluctuating between 3 and  $10 \times 10^{-6}$  after surgery, suggesting normocorticism. Indeed cortisone was stopped at 8 months (\*) after surgery. However, this state of normocorticism most likely represented mild hyperadrenocorticism which was a prelude to a recurrence of PDH 4 years after surgery. Contrast-enhanced CT images revealed no residual pituitary mass and the dog was subsequently treated medically with mitotane (o,p'-DDD).

## 6. Pituitary surgery in cats

Cushing's disease is a rare condition in cats and is usually accompanied by diabetes mellitus. Results of medical treatment of feline hyperadrenocorticism using metyrapone (Daley et al., 1993) or ketoconazole (Willard et al., 1986) have been disappointing. One report on the use of mitotane has indicated that the drug is not effective in cats (Schwedde, 1997) as it is in dogs with Cushing's disease. Bilateral adrenalectomy has been reported to be more effective than medical management in the treatment of feline Cushing's disease (Swift and Brown, 1976; Duesberg et al., 1995b), although the

prognosis is still guarded due to a high rate of post-operative complications.

As in humans and dogs, the treatment of Cushing's disease in cats should aim at eliminating the stimulus for the persisting hypersecretion of cortisol, i.e. the pituitary lesion causing excessive ACTH secretion. Hypophysectomy in the cat has long been performed in physiological and pharmacological studies. In addition, transsphenoidal selective anterior hypophysectomy in cats has been described in detail for advanced microneurosurgical training of neurosurgeons (Snyckers, 1975). However, there have been no clinical reports on its use in the treatment of feline Cushing's disease.

Microsurgical transsphenoidal hypophysectomy for the treatment of Cushing's disease was recently evaluated in 7 cats (Meij et al., 2001). Four cats had concurrent diabetes mellitus. Preoperative CT enabled accurate assessment of pituitary size (5 non-enlarged and 2 enlarged) and localization relative to intra-operative anatomical landmarks. One cat died of malignant intestinal lymphoma 2 weeks after surgery and another cat died of polycystic kidney disease and cerebrocortical necrosis 1 day after hypophysectomy. In the remaining 5 cats the hyperadrenocorticism went into remission. Hyperadrenocorticism recurred in 1 cat after 19 months but no other therapy was given and the cat died spontaneously at home 28 months after surgery. The main postoperative complications were oronasal fistula (1 cat), complete dehiscence of the soft palate (1 cat), and transient reduction of tear production (1 cat). In the 2 cats with sufficient follow-up time, the concurrent diabetes mellitus disappeared, i.e. insulin treatment could be discontinued at 1 and 5 months after hypophysectomy. In all 7 cats the histological diagnosis was pituitary adenoma. Thus microsurgical transsphenoidal hypophysectomy may be an effective treatment for feline Cushing's disease in specialized veterinary institutions with access to advanced pituitary imaging techniques. Thorough presurgical screening of cats for coexisting disease is imperative to prevent surgical mortality. More than in dogs, attention should be given to the closure of the soft palate in cats.

## 7. Conclusions

Microsurgical transsphenoidal hypophysectomy has proved to be a safe and effective treatment of Cushing's disease in dogs and cats. Pituitary surgery in a specialized veterinary institution requires a team approach involving, among others, a neurosurgeon, an endocrinologist, and a radiologist. Computed tomography (CT) of the pituitary in dogs and cats with PDH is a surgical prerequisite for localization of the gland in relation to the anatomical landmarks and for assessment of pituitary size. The neurosurgeon performing hypophysec-

tomies must master a learning curve. The surgical results compare favorably with those for mitotane therapy. With longer follow up-times recurrence rate after initially successful surgery increases. This may be because, much more so than the other cell types, the normal corticotropes present in the sella turcica after surgery tend to remain functional and may maintain normocorticism ('cure') whereas residual adenoma cells may lead to mild recurrence after relatively long periods of remission.

With the increasing availability of advanced imaging techniques such as CT and magnetic resonance imaging (MRI) in specialized veterinary institutions and further specialization in the veterinary field, it is to be expected that transsphenoidal pituitary surgery will find its place among other treatments (medical and radiotherapy) for canine and feline Cushing's disease. Comprehensive management of Cushing's disease allows the various therapeutic tools to be tailored to each particular clinical situation.

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