

## Transsphenoidal Hypophysectomy for Four Dogs with Pituitary ACTH-Producing Adenoma

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**ABSTRACT.** Four dogs diagnosed as pituitary-dependent hyperadrenocorticism were treated with transsphenoidal hypophysectomy and postoperative hormone supplementation therapy. On histological examination of the resected tissues, the tumors were ACTH-producing adenoma of the anterior lobe. Clinical signs such as alopecia and calcinosis cutis, as well as endocrinological abnormalities, were markedly alleviated after surgery. The clinical courses of these 4 dogs suggest that transsphenoidal hypophysectomy may be a useful treatment for pituitary-dependent hyperadrenocorticism.

**KEY WORDS:** canine, hyperadrenocorticism, hypophysectomy.

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Hyperadrenocorticism (HAC) is an endocrine disorder that often occurs in dogs. Of the cases in dogs, 80-85% are compromised by pituitary-dependent hyperadrenocorticism (PDH) [10]. The incidence of adrenocorticotrophic hormone (ACTH)-producing pituitary adenoma in PDH is high, and pituitary tumors have been detected at autopsy in 85% of the cases with PDH. The remaining 15% of the cases are considered to be caused by hyperplasia of corticotroph cells due to excessive stimulation by corticotropin-releasing hormone resulting from abnormalities in the hypothalamus or other parts of the central nervous system. Tumors are reported to originate in the anterior lobe of the hypophysis in 70% of the cases and in the intermediate lobe in the remaining 30% of the cases [10]. Although PDH is considered to be a tumor-associated syndrome caused by ACTH-producing pituitary tumors, this disorder has been treated primarily by suppression of adrenal cortical functions through chemotherapy [6]. In this study, 4 dogs with PDH underwent transsphenoidal hypophysectomy, and their pre- and post-operative endocrinological profiles were evaluated.

Four dogs that were suspected to have HAC were brought to the Veterinary Medical Teaching Hospital of Nippon Veterinary and Animal Science University for detailed diagnosis and treatment (Table 1). Of the characteristic clinical signs of canine HAC, polyuria-polydipsia, muscle weakness, and abdominal enlargement were observed in all 4 animals. In addition, endocrine alopecia and calcinosis cutis were noted in 3 of the 4 animals (Fig. 1). An ACTH stimulation test revealed that plasma cortisol concentrations after one-hour of ACTH administration were markedly elevated to 29.5-70.2  $\mu\text{g}/\text{dl}$  in all dogs. A high-dose dexamethasone suppression test carried out in 3 of 4 dogs demonstrated a decrease of plasma cortisol concentrations after 4 and 8 hr (Table 2). Dynamic magnetic resonance imaging (MRI) examination was performed on 3 of 4 dogs. An enlarged pituitary gland was obvious in these animals after enhance-

ment by the contrast medium (Figs. 2-A, B, C). A diagnosis of PDH was made in the 4 dogs based on the clinical signs, the findings of endocrinological examinations and the dynamic MRI of the pituitary gland mentioned above [4, 12].

Transsphenoidal hypophysectomy was conducted under general anesthesia with isoflurane in all these animals, according to the procedure reported by Meij, B.P. *et al.* [7]. Briefly, the head of each dog was elevated and fixed on the head stand in a prone position with the mouth open as wide as possible. After sterilization of the oral mucosa, the nasopharyngeal mucoperiosteum was exposed by a median incision of the soft palate. Retracting the palate with Gelpi retractors, a median incision was done, and the caudal aspect of the presphenoid and rostral aspect of the basiosphenoid bones were exposed. The base of the skull was approached by baring the center of the sphenoidal bone on the ventral side of the hypophysis using an air-drill. The distance from the origin of the pterygoid process of the sphenoidal bone to the hypophysis was determined by the MR images. When the pituitary gland and the surrounding cavernous sinus were observed through the dura mater, a dorsal incision was made and the pituitary tissue was

Table 1. Signalment of the 4 dogs in this study

Case	Breed	Age (years)	Sex	Body weight (kg)
1	Cavalier King Charles spaniel	5	Male	11.4
2	Cavalier King Charles spaniel	8	Spayed female	10.3
3	Bull terrier	5	Spayed female	17.5
4	West Highland white terrier	11	Female	8.3

Table 2. Preoperative blood chemistry and endocrinological data of the 4 dogs in this study

Case	Serum ALP (U/l)	Serum ALT (U/l)	Cortisol before/after ACTH stimulation test ( $\mu\text{g}$ of cortisol/dl of plasma)		High-dose dexamethazone suppression test ( $\mu\text{g}$ of cortisol/dl of plasma)		
			Pre	Post-1 hr	Pre	Post-4 hr	Post-8 hr
1	5000	1039	4.1	38.0	4.5	3.7	1.6
2	13735	397	3.9	31.7	5.6	3.3	3.6
3	30	67	5.1	29.5	NT	NT	NT
4	918	44	3.8	70.2	3.8	3.3	2.0

: Not tested.



Fig. 1. Preoperative appearance of Case 1. Case 1 showed the characteristic clinical signs of canine hyperadrenocorticism, including abdominal enlargement, endocrine alopecia, and calcinosis cutis.

removed by aspiration from the stalk of the hypophysis. Resection of the pituitary tissue was confirmed by visualization of the infundibulum of the third cerebral ventricle and by efflux of cerebrospinal fluid.

All 4 dogs recovered smoothly after surgery. Antibiotics were administered postoperatively (chloramphenicol 30 mg/kg, iv, bid, 5–7 days and enrofloxacin 5 mg/kg, sc, bid, 14 days), and fluid therapy was continued until the dogs maintained good hydration. Hormone supplementation therapy was initiated following hypophysectomy using antidiuretic hormone (desmopressin acetate 3–5  $\mu\text{g}$ /head, in conjunctiva, sid-bid), glucocorticoid (prednisolone 0.05–0.2 mg/kg, sid-eod), and thyroid hormone (levothyroxine sodium 15–30  $\mu\text{g}$ /kg, sid-bid) [8]. In Cases 1 and 2, transient hyperkalemia was observed after surgery, and mineralocorticoid (fludrocortisone acetate 0.0025–0.01 mg/kg, bid) was administered. During the postoperative management, Cases 3 and 4 showed visual impairment accompanied by bilateral decreases in menace reflex and light reflex after surgery. However, blindness was disappeared spontaneously within 5 days after surgery. The patients were discharged after 5–27 days of hospitalization.

Histopathology of the removed pituitary tissues, as demonstrated by hematoxylin and eosin stain, revealed abnormal proliferation of anterior lobe cells of the hypophysis in

all 4 dogs. The tumors were diagnosed based on their staining characteristics to be eosinophilic cell tumor of the anterior lobe in 3 of the 4 dogs and chromophobic cell tumor in 1 dog (Fig. 3). Immunohistochemistry, using antibodies to anterior pituitary hormones, revealed that the cells were positive against anti-ACTH antibody but negative against anti-GH, anti-TSH, anti-LH, and anti-FSH antibodies. On the basis of these observations, a diagnosis of ACTH-producing adenoma of the anterior lobe of hypophysis was made (data not shown).

Table 3 shows the blood chemistry and endocrinological profiles of the 4 dogs at 79–354 days after surgery. High hepatic enzyme values and the high cortisol values in the ACTH stimulation test were much improved in all dogs when compared to the preoperative values. Namely, plasma cortisol concentrations after one-hour of ACTH administration were markedly decreased to 2.7–18.9  $\mu\text{g}/\text{dl}$  in all dogs. Endocrine alopecia and calcinosis cutis, which were observed preoperatively in Cases 1, 2, and 4, were also alleviated progressively after surgery and were nearly disappeared at 3–6 months after surgery (Fig. 4).

Among the pituitary adenomas observed in canine PDH, approximately 50% of the cases are microadenomas of less than 3 mm in diameter, while approximately 10–15% are macroadenomas greater than 10 mm in diameter [10]. Macroadenoma or adenocarcinoma is an intracranial space-occupying lesion. Therefore, patients with these lesions have been reported to develop central nervous system signs such as listless attitude, inappetence, aimless wandering, ataxia, head pressing, circling, behavioral alterations, and loss of body temperature regulation due to compressive damage of the hypothalamus [2, 9]. In 3 of the 4 dogs examined in this study, the size of pituitary gland evaluated by dynamic MRI before surgery was 10–12 mm, but none of the dogs exhibited the preoperative neurological signs. Temporary visual impairment developed in Cases 2 and 4 for about 5 days after surgery. These visual disturbances may be caused by empty sella due to falling of the optic nerve, which had been dorsally displaced by the enlarged pituitary tissue, into the pituitary fossa [5].

Case 1 showed bilateral facial paralysis prior to surgery. This condition may be attributed to demyelinating lesions of the facial nerve caused by secondary hypothyroidism, since the serum concentration of T4 and free T4 was reduced

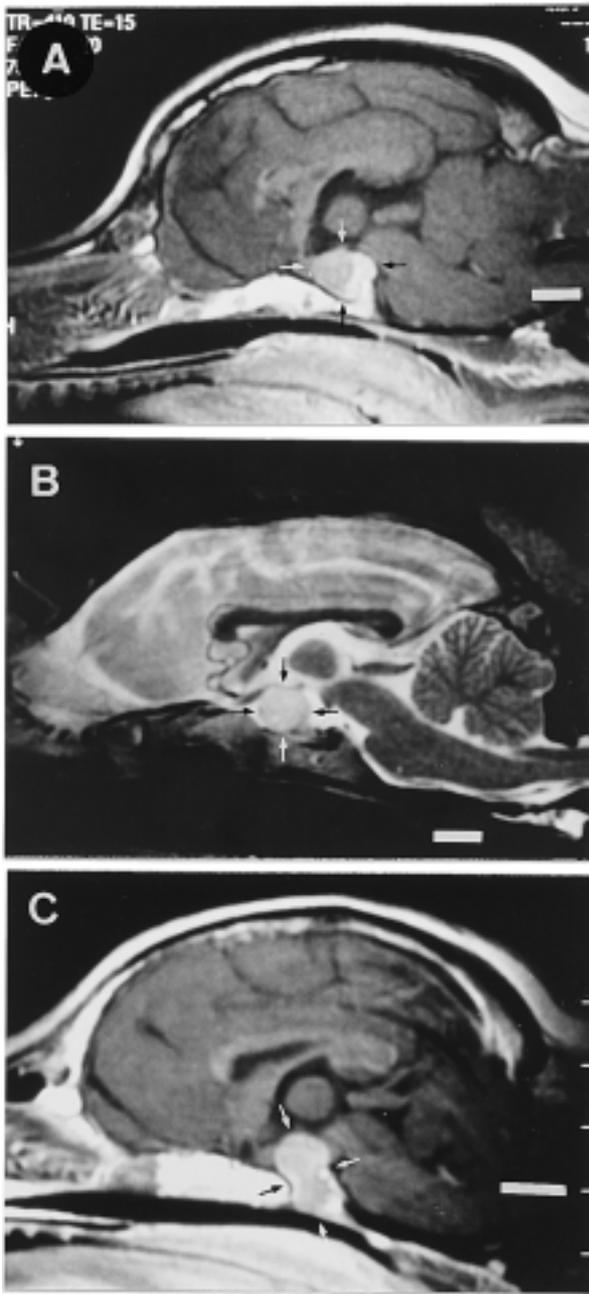


Fig. 2. Gadolinium (Gd)—enhanced magnetic resonance imaging (MRI) of the dogs presented in this study. 2-A: Gd-enhanced T1-weighted image of the Case 2. 2-B: Gd-enhanced T2-weighted image of the Case 3. 2-C: Gd-enhanced T1-weighted image of the Case 4. An enlarged pituitary gland was shown by arrows, and a horizontal white bar represents 10 mm on each image, respectively. In all cases, an enlarged pituitary mass that compressed the hypothalamus was confirmed. In Case 4 (Fig. 2-C), the pituitary mass was enlarged toward the ventral direction, invading the sphenoidal bone.

before surgery. The facial paralysis was alleviated by the administration of a T4 preparation, and the number of TSH-

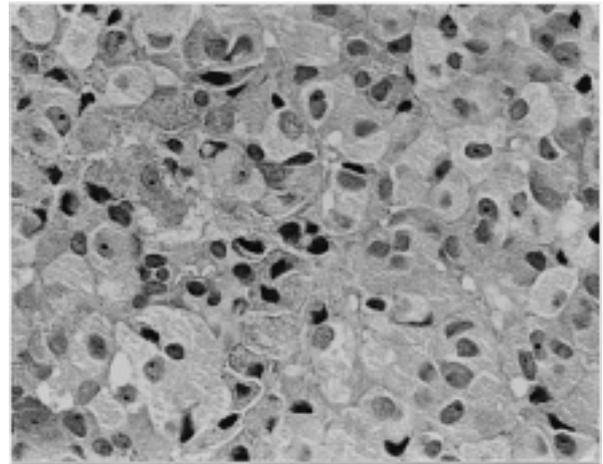


Fig. 3. Histological finding of the tumor harvested during the surgery in Case 2. The tumor is composed of well-differentiated, large or small chromophobic cells.

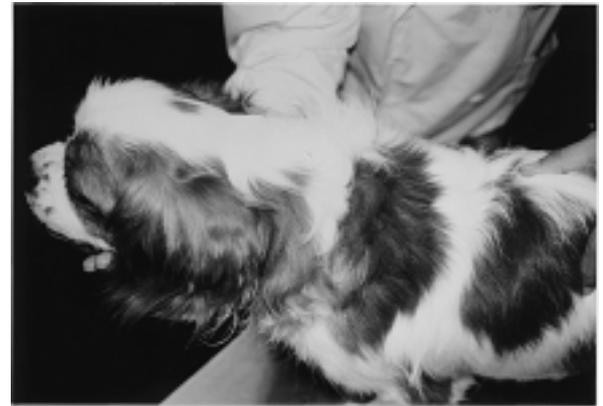


Fig. 4. Gross appearance of Case 1 (as the same dog as Fig. 1) at 5 months after the hypophysectomy. The systemic skin abnormalities observed prior surgery gradually remitted and were almost resolved at 5 months of the surgery.

Table 3. Current data on blood chemistry and cortisol values before and after ACTH stimulation

Case	Days after surgery (day)	Serum ALP (U/l)	Serum ALT (U/l)	Cortisol before/after ACTH stimulation test (µg of cortisol/dl of plasma)	
				Pre	Post-1hr
1	330	196	40	2.5	8.5
2	354	557	25	0.5	2.7
3	87	65	47	1.9	7.5
4	79	470	21	2.2	18.9

producing cells observed in association with proliferation of ACTH-producing adenoma cells in the resected pituitary tissues was reduced [3].

Canine PDH has been commonly treated by selective destruction of the zona fasciculata with o,p'-DDD [6, 10]. However, Bertoy, E.H. *et al.* reported that the volume of the

pituitary tumor increased after 1 year in about half of the dogs (7/13) treated with o,p'-DDD [1]. In humans, Nelson's syndrome may appear after adrenalectomy for the treatment of PDH, in which negative feedback to the anterior lobe of hypophysis is abolished due to reduced cortisol production to promote the growth of pituitary tumors. In small animals, Nelson, R.W. *et al.* also suggested that Nelson's syndrome must be considered when neurological signs occur shortly after the beginning of o,p'-DDD treatment [9]. Two (Cases 1 and 3) of the 4 dogs presented in this study had undergone o,p'-DDD therapy (5–30 mg/kg) before hypophysectomy for 21 and 51 days, respectively. They showed a recurrence of clinical signs, such as polyuria-polydipsia, or exacerbation of the general condition after o,p'-DDD therapy.

Transsphenoidal hypophysectomy for canine PDH was first reported by Rijnberk, A.D. *et al.* in 1968 [11]. In 1998, Meij, B.P. *et al.* presented excellent results of hypophysectomy in 52 cases of PDH [8]. In this study, clinical signs and endocrinological data were markedly alleviated after transsphenoidal hypophysectomy in all of the dogs. Although we did not measure the plasma ACTH level, the alleviation of these clinical signs and the response of cortisol in the ACTH stimulation test after surgery must be attributed to hypophysectomy. In conclusion, transsphenoidal hypophysectomy as a treatment for PDH caused by ACTH-producing adenoma of the pituitary gland is quite useful in dogs.

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