Hypophysectomy for a Dog with Coexisting Cushing’s Disease and Diabetes Mellitus

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ABSTRACT. An 11-year-old male mixed breed dog diagnosed with Cushing’s disease and diabetes mellitus was treated by hypophysectomy. After surgery, the hypercortisolemia disappeared and the diabetes status improved. The insulin requirement to control hyperglycemia gradually decreased. At 12 weeks after surgery, there was no requirement for insulin and we suspected the diabetes was completely resolved. In the present case, diabetes mellitus seems to be secondary to Cushing’s disease. In conclusion, this mixed breed dog with coexisting Cushing’s disease and diabetes mellitus is the first case showing the effectiveness of hypophysectomy to treat diabetes mellitus secondary to Cushing’s disease in dogs.

KEY WORDS: canine, Cushing’s disease, diabetes mellitus, hypophysectomy, pituitary.

Spontaneous hyperadrenocorticism (HAC), or Cushing’s syndrome, is a common endocrine disease in dogs that results from excessive cortisol secretion by the adrenal cortex. Approximately 80–85% of HACs in dogs are pituitary-dependent HACs (PDH), due to adrenocorticotropic (ACTH)-secreting corticotrophic adenoma, and 15–20% of cases are adrenocortical-dependent due to a glucocorticoid-secreting adenocortical tumor [8]. The characteristic symptoms of HAC are polydipsia, polyuria, abdominal distention and skin lesions such as alopecia and calcification. Serious and life-threatening secondary complications and comonitant diseases may occur in HAC dogs because of the long-term hypercortisolism. Hypertension, congestive heart failure, pancreatitis, pylonephritis, glomerulonephritis, pulmonary thromboembolism and diabetes mellitus (DM) have been reported as diseases secondary to HAC [23]. Altered glucose metabolism and insulin resistance caused by glucocorticoid excess are common features of HAC in dogs. In a previous study, approximately 40–60% of dogs with HAC had fasting hyperglycemia, whereas 5–10% of dogs with HAC had overt DM [8, 23]. Although medical management of concurrent DM and HAC in dogs has been studied [25], surgical treatment has not been reported.

In the present study, we report a dog with concurrent DM and PDH that was treated with transphenoidal hypophysectomy; remission of both diseases occurred after surgery. An 11-year-old, male, mixed breed dog weighing 8.7 kg was referred to the Veterinary Medical Teaching Hospital of Nippon Veterinary and Life Science University with complaints of polyuria, polydipsia, polyphagia, abdominal enlargement, dorsal alopecia and poor wound healing. The case had been treated for 1 year with 3.0–6.9 mg/kg/day trilostane (DESOPAN®, Mochida Pharmaceutical, Tokyo, Japan) and 8–18 IU/day insulin glargine (LANTUS®, Sanofi-Aventis, Tokyo, Japan) before admission to the hospital [2, 21]. At the first visit, the dog was being treated twice-daily with 7 IU of insulin glargine by subcutaneous injection, and 3.4 mg/kg trilostane orally. There was no abnormality on thoracic radiography, but abdominal radiography revealed hepatomegaly. Routine laboratory examination showed lymphopenia (lymphocytes: 332/μl, reference range: 800–3,800/μl) and increased concentrations of glucose, alanine aminotransferase and alkaline phosphatase. Other biochemical variables were within the reference ranges (Table 1). Urine specific gravity was low (1.009). Urinalysis revealed glucosuria and bacterial cystitis. The history, clinical signs and laboratory findings suggested that this case had HAC and DM.

To evaluate the function of the pituitary-adrenocortical axis, plasma ACTH concentrations and serum cortisol concentrations were assayed as previously described [10, 11, 28]. The basal plasma ACTH concentration was 217 pg/ml (reference range: 6.0–58.0 pg/ml). An ACTH-stimulation test was performed by collecting blood samples to measure cortisol concentrations at 0 and 60 min after intravenous administration of 0.25 mg of synthetic ACTH (Cortrosyn®, Daiichi Sankyo, Tokyo, Japan). The basal (0 min) and post-ACTH (60 min) serum cortisol concentrations were 1.6 pg/dl (reference range: 0.5–6.0 μg/dl) and 2.2 μg/dl (reference range: 0.5–6.0 μg/dl).
range: 6.0–17.0 \( \mu g/dl \), respectively. The results showed that HAC was well-controlled by trilostane. The serum total thyroxine (T4), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) concentrations were assayed as previously described [10, 28] and were within the reference ranges (total T4: 19.2 nmol/l, reference range 13.0–51.0 nmol/l; FT4: 21.1 pmol/l, reference range 6.6–40.0 pmol/l; TSH: 0.09 ng/ml, reference range 0.03–0.38 ng/ml).

Magnetic resonance imaging of the pituitary fossa was performed under anesthesia with a 1.5 Tesla superconducting magnet (VISART, Toshiba Medical System Corporation, Tokyo, Japan) as previously described [32]. T1-weighted transverse scans and sagittal scans of the skull were obtained with a 410-ms repetition time, 15-ms echo time and 2.0-mm-thick consecutive slices. Contrast-enhanced T1 transverse images showed the pituitary gland was enlarged (height, 6.0 mm; pituitary height/brain area ratio, 0.37; Fig. 1) [15]. A microadenoma of the pituitary was suspected, and transsphenoidal hypophysectomy was performed on the 15th day after the first visit, as previously described [16, 17].

Histological examination of the resected pituitary revealed an adenoma. HE staining showed that the adenoma cells had irregular nuclei. Immunolabeling revealed that the adenoma was immunoreactive for ACTH (Fig. 2). Based on these findings, we diagnosed the case as a corticotroph pituitary adenoma.

After resecting the entire pituitary, hormone replacement therapy was prescribed and consisted of desmopressin, the synthetic arginine vasopressin (AVP) with 0.1 \( \mu g/kg \) every 12 hr for 2 days postoperatively, cortisone acetate with 1 mg/kg/day and thyroxine with 40 \( \mu g/kg/day \), as previously described [13, 16]. Over a period of 4 weeks, the dose of cortisone acetate was gradually lowered to 0.5 mg/kg/day. And the dose of cortisone acetate was tapered and withdrawn by 9 weeks after the surgery. After surgery, the
hypercortisolemia disappeared and DM improved. An ACTH-stimulating test and measurement of plasma ACTH concentration were performed at 2 weeks from the surgery, the results showed successful hypophysectomy and remission of the hypercortisolemia (Table 2). The requirement for insulin glargine to control hyperglycemia gradually decreased from 14 IU/day before surgery to 6 IU/day at 8 weeks after surgery, and was not needed at 12 weeks after surgery; therefore, we suspected the DM had been resolved (Fig. 3). At the time of writing, 20 months after surgery, the dog is still alive and only receiving 40 μg/kg/day thyroxine.

Hyperglycemia is frequently observed in HAC dogs. In previous studies, approximately 40–60% of dogs with HAC had fasting hyperglycemia [6, 8, 23]. Factors that affect glucose metabolism in dogs with glucocorticoid excess include increased hepatic gluconeogenesis and decreased peripheral utilization of glucose by antagonizing the effect of insulin [24, 26]. In addition, glucocorticoids inhibit glucose-stimulated insulin secretion from pancreatic β cells in mice [4], but about one half of dogs with HAC exhibit abnormally increased insulin secretion [6, 20], which may be caused by aggressive gluconeogenesis in these dogs. Insulin resistance, the presence of endogenous hyperinsulinemia in normal or high plasma glucose concentrations, is also a common feature of dogs with HAC [24, 26]. It has been shown that a chronic excess in circulating cortisol causes symptoms of HAC and induces pre or subclinical diabetes in dogs [8, 9]. In humans, it is quite common for glucocorti-

Table 2. Results of ACTH-stimulation tests and measurements of plasma ACTH concentrations

<table>
<thead>
<tr>
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<th>Basal-ACTH (pg/ml)</th>
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<tr>
<td>Before starting trilostane treatment</td>
<td>–</td>
</tr>
<tr>
<td>During trilostane treatment</td>
<td>217</td>
</tr>
<tr>
<td>After 2 weeks from Hypophysectomy</td>
<td>8.7</td>
</tr>
<tr>
<td>Reference ranges</td>
<td>6.0–58.0</td>
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Fig. 2. Immunohistochemistry of resected pituitary tissue using an anti-ACTH antibody. Hematoxylin-eosin staining (A, C) and anti-ACTH immunoreactivity (B, D) in sections of the resected pituitary tissue. The arrows in A and B indicates location of C and D, respectively. Adenoma cells with strong cytoplasmic immunoreactivity to an anti-ACTH antibody are observed. Bar=500 (A, B) and 50 (C, D) μm.
coids to cause whole-body insulin resistance [1, 27]. However, only 5–10% of dogs with HAC have overt DM, and insulin-independent diabetes is rare in the dogs [8, 9, 23]. In most dogs with HAC, the increased insulin secretion partly controls blood glucose but may not be sufficient to completely normalize blood glucose. By contrast, diabetes frequently occurs in cats and humans with HAC [1, 9, 27].

According to the underlying pathological condition, hypercortisolemia may cause insulin-independent or severe insulin-dependent diabetes in dogs with HAC. Therefore, in coexisting HAC and DM, normalizing the hypercortisolemia with either surgical or medical treatment will affect the secondary DM. If the concurrent DM is insulin-dependent, and if HAC was responsible for the insulin resistance, normalizing hypercortisolemia may increase insulin sensitivity and reduce the insulin requirement. Similarly, in insulin-independent DM, a reduction in insulin requirements or remission of diabetes may occur. In fact, dogs with concurrent HAC and DM showed reduced insulin requirements during treatment with mitotane (o,p′-DDD [dichlorodiphenylchloroethane]), a specific adrenocorticolytic drug [25]. In that study, eight of 11 dogs treated with o,p′-DDD showed reduced insulin requirements. On the other hand, it has been reported that 5% of these dogs may not require insulin if PDH can be well controlled [8, 23]. Trilostane, a competitive inhibitor of 3β-hydroxysteroid dehydrogenase, was recently reported to be a safe and effective alternative to o,p′-DDD in dogs with PDH [22, 28]. However, no reports have described the effect of trilostane on concurrent DM but, based on this case report, the effects will be similar to o,p′-DDD. Humans with HAC treated with selective trans-sphenoidal hypophysectomy, and cats with HAC treated with total hypophysectomy showed improvements in insulin resistance [18, 30]. However, there are no reports of hypophysectomy for coexisting PDH and DM in dogs.

Until recently, the goal of PDH treatment was to eliminate the clinical signs caused by hypercortisolemia using drugs such as mitotane or trilostane. Although these treatments are effective, they are not directed at the ACTH-secreting pituitary adenoma. The pituitary tumor may continue to expand, which may lead to neurological signs due to the intracranial mass effect [3, 5]. Ideally, the treatment of PDH in dogs should be directed at the tumor. A decade ago, transsphenoidal hypophysectomy was introduced as a treatment for canine PDH, and was proven to be an effective approach [16]. Furthermore, it has been reported that hypophysectomy is associated with a longer survival time than mitotane treatment [12, 16]. Hypernatremia, diabetes insipidus and secondary hypothyroidism were the main complications present after surgery [13, 16]. These complications are due to the removal of the posterior pituitary, which releases AVP, and the anterior pituitary, which includes thyrotropic cells. However, these complications can be controlled by hormone replacement therapy such as synthetic AVP or thyroxine and transfusion with low sodium solutions [13, 16]. In addition, we consider that dogs with PDH are candidates for surgery if their pituitary height is smaller than 12 mm, and if the dog is in a good physical condition, capable of tolerating anesthesia. Notably, in dogs with PDH, larger pituitary tumors are associated with higher recurrence rates and surgery may only offer a palliative treatment [12]. In the present case, the pituitary height was 6 mm and the dog was in a good physical condition. Therefore, we suggested hypophysectomy for the dog’s owner because of the anticipated longer survival time and potential for PDH remission.

It is important to investigate the effect of hypophysectomy in dogs with coexisting PDH and DM. In the present case, we diagnosed the concurrent DM as secondary to PDH because of the improvement and remission of diabetes after hypophysectomy. If the diabetes was not secondary to PDH, an apparent reduction in the insulin requirement may not have occurred. Normalizing hypercortisolemia by hypophysectomy, in the present case eliminated the insulin resistance and induced the remission of secondary diabetes. Interestingly, trilostane treatment successfully inhibited the secretion of cortisol to below the reference range after ACTH stimulation, but was not sufficient to induce the remission of diabetes. Furthermore, the results of the ACTH-stimulating test at 2 weeks after surgery was not much different from the one performed during trilostane treatment (Table 2). With trilostane treatment, the inhibition of cortisol secretion may increase ACTH production and secretion in pituitary corticotroph adenoma [33]. Also, there is a possibility that cortisol secretion inhibitory effect vary with time after an administration of trilostane. Thus, trilostane treatment may not have normalized the cortisol secretion throughout the day. By contrast, removing the

Fig. 3. Changes in blood glucose concentration before meals and the daily insulin glargine requirement to control hyperglycemia before and after hypophysectomy. The insulin glargine requirement decreased gradually after surgery.
corticotroph adenoma by hypophysectomy results in the absence of pituitary ACTH secretion, and reduced adrenocorticotropic may control the cortisol secretion throughout the day. Therefore, these speculations may explain that trilostane treatment failed to eliminate insulin resistance, whereas hypophysectomy successfully treated the secondary DM in the present case. To our knowledge, the present case is the first dog with DM and PDH to be treated with hypophysectomy. Accordingly, it remains to be seen if transsphenoidal hypophysectomy can successfully treat dogs with coexisting DM and PDH. The effectiveness of this approach may depend on the insulin secretory capacity from pancreatic $\beta$ cells. Measuring the serum insulin concentration may help to predict whether hypophysectomy will affect the secondary diabetes in these dogs.

In conclusion, to our knowledge, this is the first case report of coexisting PDH and DM showing that transsphenoidal hypophysectomy successfully treated DM secondary to PDH in dogs. Hypophysectomy may improve not only the hypercortisolism, but also the secondary DM.

REFERENCES


