Magnetic Resonance Imaging Assessment of Pituitary Posterior Lobe Displacement in Dogs with Pituitary-Dependent Hyperadrenocorticism

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ABSTRACT. The displacement and signal intensity (SI) of the pituitary posterior lobe were evaluated on T1 weighted magnetic resonance (MR) images in 28 dogs with pituitary dependent hyperadrenocorticism (PDH). Compared with normal dogs, the posterior lobe was displaced dorsally in the pituitary of the PDH dogs. Correlation between the pituitary height/brain area (P/B) ratio and the displacement of the posterior lobe in the PDH dogs suggests that dorsal displacement of the posterior lobe increases in accordance with enlargement of the pituitary. As to the SI of the posterior lobe, the PDH dogs showed significantly lower SI in comparison to the normal dogs. Taken together, these results suggest that assessment of the displacement and SI of the posterior lobe of the pituitary on T1-weighted MR images is useful for the diagnosis of pituitary adenoma. In pituitary microadenoma that presents no apparent tumorigenesis on MRI, evaluation of these values may be useful for diagnosis and selection of an appropriate therapy.

KEY WORDS: hyperadrenocorticism, MRI, pituitary posterior lobe, signal intensity.

Full Paper

Approximately 80% of cases of pituitary-dependent hyperadrenocorticism (PDH), a major endocrine disease in dogs, are caused by pituitary tumors [adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma]. For diagnosis of pituitary tumors, visualization of the pituitary gland by computed tomography (CT) and/or magnetic resonance imaging (MRI), which allow noninvasive examination of minute lesions in the brain, are useful. These imaging methods distinguish enlargements of the the pituitary tumor by measuring the pituitary height/brain area (P/B) ratio and enable classification of lesions as macroadenoma or microadenoma. Diagnosis based on this classification enables selection of an appropriate therapy [4, 6, 14, 17]. However, some cases of pituitary tumors have no apparent tumorigenesis, especially in the case of microadenoma. Therefore, diagnosis in these PDH dogs may be difficult.

One of the characteristics of the pituitary gland is high signal intensity (SI) of the posterior lobe on noncontrast T1-weighted MR images [2, 16, 19]. High SI is observed in the normal pituitary of healthy animals and may be used to determine the spatial position of the posterior lobe within the pituitary [5, 20]. In addition, the SI of the posterior lobe may reflect the density of secretory granules containing arginine vasopressin (AVP), implying that the SI is closely associated with the state of water metabolism of the animal [15, 16]. In the MRI examination of the PDH dogs in our study, hypointensity of the posterior pituitary lobe was confirmed. Furthermore, the dogs with an enlargited pituitary showed an altered position of the posterior lobe within the pituitary compared with healthy dogs. In this study, we investigated the relationship between enlargement of the pituitary and the position and SI of the pituitary posterior lobe of the pituitary using MRI examination of the PDH dogs. In addition, we examined the usefulness of these parameters as a diagnostic method for evaluation of pituitary tumors.

MATERIALS AND METHODS

PDH cases and normal dogs: Twenty-eight dogs presented to the Animal Medical Center of Nippon Veterinary and Life Science University were used as the PDH clinical case group (PDH group). In these dogs, the diagnosis of hyperadrenocorticism was based upon the results of their history, physical examination and the results of CBC and serum biochemical analysis. The diagnosis of hyperadrenocorticism was also confirmed by an ACTH stimulation test. Pituitary-dependent hyperadrenocorticism was confirmed by detection of two equally sized enlarged adrenal glands on abdominal ultrasonography [3, 10, 11]. The mean age and weight of the PDH group were 9.4 ± 2.2 years old (mean ± SD) and 11.5 ± 6.1 kg, respectively. The group consisted of 8 males (2 of them were castrated) and 20 females (10 of them were sterilized) of various breeds, including the Shih Tzu, Cavalier King Charles Spaniel, Yorkshire Terrier, Miniature Dachshund, Toy Poodle, Pembroke Welsh Corgi, Beagle, Siberian Husky, Shiba and Kai, and mongrels.

The normal group consisted of 18 adult dogs determined to be healthy by their clinical conditions and the results of blood tests, biochemical examination of blood and an ACTH stimulation test. The mean age and weight of the
dogs in the normal group were 2.6 ± 1.4 years old and 10.7 ± 1.7 kg respectively, and the group consisted of 9 males and 9 females. All of the dogs of the normal group were Beagles.

Experimental protocol: All the dogs in the PDH and normal groups were examined by MRI scans of the head. P/B ratios were calculated based on the MR images of all the animals and were compared between the groups. The dogs in the PDH group were classified into 2 groups—those with an enlarged pituitary (the enlargement group; P/B ratio greater than 0.31) and those with nonenlarged pituitary glands (the nonenlargement group; P/B ratio smaller than 0.31) [14]. The spatial position of the posterior lobe within the pituitary in the craniocaudal, dorsoventral and lateral direction were examined by MRI in all the animals. Measurements in each direction were compared between the PDH and normal groups or between the enlargement and nonenlargement groups. The correlation between the P/B ratio and each measurement representing the position of the posterior lobe within the pituitary was also examined in the PDH group. Furthermore, the SI values for the pituitary posterior lobe in MRI were measured and compared between the PDH group and the control group or between the enlargement group and the nonenlargement group.

The 9 animals in the PDH group were treated by hypophysectomy on the basis of a head MRI examination. The removed pituitary glands were processed for pathological examination, and all 9 animals in the PDH group were confirmed as having an ACTH adenoma.

Head MRI examination: Head MRI was performed for the PDH and normal groups in sternal recumbency using a superconducting magnet type 1.5T MRI system (Visart, Toshiba Medical Systems Corporation, Tokyo, Japan) with a human knee coil. All the animals were examined under general anesthesia. After pretreatment with droperidol (Droleptan, Daiichi Sankyo Co., Ltd., Tokyo, Japan), anesthesia was induced with propofol (Rapinovet, Takeda Pharmaceutical Co., Ltd., Tokyo, Japan) and oxygen under controlled respiration.

Transverse scans were performed perpendicular to the skull base from the rostral clinoid processes to the dorsum sellae. Sagittal and parasagittal sections were also made through the pituitary fossa. Transverse and sagittal T1-weighted spin echo images (TR/TE = 410/15 ms, 2 mm slice thickness without inter slice gap, 256 × 256 matrix, 12 cm field of view, four signals acquired and an imaging time of 8 min 45 sec) were obtained. Contrast-enhanced T1 weighted images were acquired with the same setting for the pulse sequence immediately after intravenous injection of a bolus of 0.2 ml/kg of gadodiamide hydrate (Omniscan, Dainippon Sumitomo Pharma Co., Ltd., Tokyo, Japan) and oxygen under controlled respiration.

Measurement of displacement of the pituitary posterior lobe: From the T1-weighted MR images of the sagittal and transverse planes for each animal in the PDH and normal groups, one image was chosen that contained the largest crosssection of the pituitary. Displacement of the posterior lobe within the pituitary in the craniocaudal direction was measured on the selected sagittal image (Fig. 2A). Initially, a tangent to the hypophyseal fossa, which was drawn parallel to the line tangent to both the apex of the dorsum sellae and the ridge of the sphenoid bone, was regarded as the transverse axis. A tangent to the apex of the dorsum sellae perpendicular to this transverse axis was regarded as the longitudinal axis. Then, the distances from the longitudinal axis to the anterior end of the posterior lobe and to the posterior end of the posterior lobe were measured (Fig. 2B). The distance between the transverse axis and the line tangent to both the dorsum sellae and the sphenoid ridge was measured as the height of the dorsum sellae (ds).

Displacement of the posterior lobe in the dorsoventral and lateral directions within the pituitary gland was measured on the selected transverse images (Fig. 3A). Initially, the median line of the cerebrum and diencephalon was regarded as the longitudinal axis, and a tangent to the bottom of the hypophysial fossa perpendicular to the longitudinal axis was regarded as the transverse axis. Then, each distance from the transverse axis to the superior end and from the transverse axis to the inferior end of the posterior lobe was measured (Fig. 3B). Each distance from the longi-
Measurement of the displacement of the pituitary posterior lobe on T1-weighted sagittal images. (A) The displacement of the pituitary posterior lobe in the craniocaudal direction in the pituitary gland was measured on sagittal images. (B) Initially, a tangent to the hypophyseal fossa that was drawn parallel to the line tangent to both the dorsum sellae and the sphenoid ridge was regarded as the transverse axis. A tangent to the dorsal top of the dorsum sellae perpendicular to this transverse axis was regarded as the longitudinal axis. Then, the distances from the longitudinal axis to the anterior end of the posterior lobe and to the posterior end of the posterior lobe (Sa and Sp, respectively) were measured. The distance between the transverse axis and the line tangent to both the dorsum sellae and the sphenoid ridge was measured as the height of the dorsum sellae (ds).

Fig. 3. Measurement of the displacement of the pituitary posterior lobe on T1-weighted transverse images. (A) Displacement of the posterior lobe in the dorsoventral and lateral directions in the pituitary gland was measured on transverse images. (B) Initially, the median line of the cerebrum and diencephalon was regarded as the longitudinal axis, and a tangent to the bottom of the hypophyseal fossa perpendicular to the longitudinal axis was regarded as the transverse axis. Then, the distances from the transverse axis to the superior end of the posterior lobe and the inferior end of the posterior lobe (Td and Tv, respectively) and the distances from the longitudinal axis to the right end and to the left end of the posterior lobe (Tr and Tl, respectively) were measured.

These displacement values in each direction were abbreviated as Sa and Sp (distance from the longitudinal axis to the anterior and posterior end of the posterior lobe, respectively); Td and Tv (distance from the transverse axis to the superior and inferior end of posterior lobe, respectively); and Tr and Tl (distance from the longitudinal axis to the right and left end of the posterior lobe, respectively). These methods for measurement of the displacement values were developed by us.

Measurement of the SI ratio of the posterior lobe: In the PDH and control groups, the SI ratios of the posterior lobe were measured, as previously described [22]. The SI value was measured at the posterior lobe and the cerebral cortex by MRI computer software on the T1-weighted transverse MR images. SI ratios were calculated according to the following formula to standardize for the difference in the conditions of MRI scanning: SI ratio = (SI value of the posterior lobe) / (SI value of the cerebral cortex). The SI ratios were compared between the PDH and control groups, as well as between the enlargement and nonenlargement groups in the PDH group in order to assess the effects of PDH and enlargement of the pituitary on the SI of the pituitary posterior lobe.

Surgical resection of the pituitary gland: For the 9 cases that underwent surgical treatment, transsphenoidal hypophysectomy was conducted according to the method reported previously [12]. Pituitary tissues were fixed in 4% paraformaldehyde at 4°C for 24 hr, embedded in paraffin
and cut into thin sections. For pathological examination, the tissue sections were stained with hematoxylin and eosin (HE) staining. Immunohistochemical staining was conducted using anti-human ACTH antibody by the following methods [21]. For immunohistochemistry, the tissue sections were deparaffinized in xylene and rinsed with 100% ethanol. After endogenous peroxidase was blocked with 0.3% H₂O₂ at room temperature for 30 min, the sections were rinsed with 0.01 M phosphate buffered saline (PBS). Anti-ACTH antibody [monoclonal anti-human adrenocorticotropic IgG, mouse; Dako Denmark A/S, Glostrup, Denmark] was placed on the tissue sections, and reacted at 4°C overnight. After the sections were rinsed with PBS, antimouse antibody [anti-mouse IgG, sheep, F(ab’)_2; GE Healthcare Bioscience Co., Piscataway, NJ, U.S.A.] was added to the sections as the secondary antibody and reacted at room temperature for 30 min. The sections were then rinsed with PBS, and the antigen-antibody complexes were rendered visible by reaction in 50 mM Tris-HCl buffer (pH7.6) containing 0.05% 3,3’-diaminobenzidine-4HCl (DAB). The sections were also stained with methyl green for 30 min for nuclear staining.

Methods of analysis: The P/B ratios were compared between the PDH and control groups using the Mann-Whitney U test. Displacement values for the pituitary posterior lobe in each direction (Sa, Sp, Td, Tv, Tr and Tl) were compared between the PDH and normal groups and between the enlargement and nonenlargement groups using the Mann-Whitney U test. Correlations between the displacement values in each direction and P/B ratio in the PDH group were tested using Pearson’s correlation coefficient in order to assess the effect of enlargement of the pituitary gland on the posterior lobe. SI ratios of the pituitary posterior lobe were compared between the PDH and normal groups and between the enlargement and nonenlargement groups using the Mann-Whitney U test. *P<0.05 was considered statistically significant.

RESULTS

P/B ratio: The P/B ratios were significantly higher in the PDH group than in the normal group (mean ± SD, respectively: 0.401 ± 0.166 and 0.248 ± 0.047, *P<0.001). The P/B ratio was greater than 0.31 in 20 of 28 cases (71.4%) in the PDH group.

Displacement of the pituitary posterior lobe: The Td and Tv of the posterior lobe were significantly higher in the PDH group than in the normal group (Fig. 4). In the PDH group, the Td of the posterior lobe was 1.218 ± 0.618 (mean ± SD), and the Tv was 0.582 ± 0.428. In the normal group, the Td of the posterior lobe was 0.830 ± 0.147, and the Tv was 0.280 ± 0.103. There was no significant difference in other displacement values.

Comparison between the enlargement group and nonenlargement group showed no significant difference in any displacement value (Fig. 5).

Correlation between displacement of the posterior lobe and P/B ratio: With regard to correlations between the displacement values of the posterior lobe in each direction and P/B ratio, Tr, Tl, Td and Tv were correlated significantly with the P/B ratio (r=0.667, *P<0.001; r=0.614, **P<0.001; r=0.864, ***P<0.001; and r=0.851, ***P<0.001, respectively; Fig. 6).

SI ratio of the pituitary posterior lobe: The SI ratios of the posterior lobe in the normal and PDH groups were 2.004 ± 0.355 (mean ± SD) and 1.646 ± 0.208, respectively. The SI ratio of the PDH group was significantly lower than that of the normal group (*P<0.05). The SI ratios of the posterior lobe in the enlargement and nonenlargement groups were 1.657 ± 0.237 and 1.624 ± 0.178, respectively. There was no significant difference between the groups.

Pathological examination: Nine dogs in the PDH group were chosen to undergo resection of the pituitary, and transsphenoidal hypophysectomies were conducted. Resected pituitary glands were stained with hematoxylin and eosin...
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(HE) and subjected to immunohistochemical staining. In the HE staining sample, cellular foci with enlarged basophilic cytoplasm and irregular nuclei were observed (Fig. 7A). Immunohistochemistry revealed that these cellular foci were immunoreactive for anti-ACTH antibody (Fig. 7B).

Discussion

CT and MRI provide a lot of information, such as the size and morphology of the enlarged pituitary gland, the presence of pituitary tumors and the position of the pituitary tumor in the cranial cavity, which is very useful for deciding the treatment for PDH. Generally, it has been recognized that the size of the pituitary varies depending on the physical size of an individual dog, even within the same breed [13]. In a previous report, it was demonstrated that the P/B ratio enabled adjustment for the size of dog in order to assess the presence of an enlargement of the pituitary in each clinical case [14]. The P/B ratio allows for quantification of pituitary enlargement. However, more than half of PDH lesions are microadenomas smaller than 10 mm in diameter, which may not be necessarily detected as pituitary enlargement. Thus, it has been difficult to diagnose PDH by measuring only the size of the pituitary on CT or MR images.

To date, no report has examined the imaging characteristics of the pituitary posterior lobe in healthy dogs. Anatomically, the posterior lobe is located slightly to the dorsal side of the center of the pituitary. This area is clearly revealed on T1-weighted MR images due to the high signal intensity shown by the posterior lobe [7, 8, 13].

In this study, we examined the localization of the pituitary posterior lobe in clinical cases of PDH using the displacement values of the posterior lobe in each direction. Compared with the normal group, the posterior lobes of the pituitary were observed to be displaced in the dorsal direction in the PDH group. Anatomically, a large proportion of the pituitary anterior lobe is located on the cranioventral side of the pituitary intermediate and posterior lobes. It is possible that when the anterior lobe is enlarged and presses upon the surrounding tissues as a result of a developing adenoma of the corticotroph cells in the cranioventral anterior lobe, the posterior lobe is pushed in the dorsocaudal direction. However, the posterior lobe may be displaced dorsally due to an obstruction of the dorsum sellae in the caudal direction. In comparison of the displacement values between the enlargement group and nonenlargement group, no significant difference was observed. This result suggests that measurement of displacement values in the dorsal direction has the potential to aid in the diagnosis of PDH regardless of microadenoma or macroadenoma. In the correlation between the P/B ratio and the displacement values of the
posterior lobe in the PDH group, the displacement values in the right and left lateral, dorsal and ventral directions demonstrated significant correlation with the P/B ratio. These results suggest that the displacement of the posterior lobe increases in accordance with pressure in the dorsal direction caused by enlargement of the pituitary gland. In addition, the posterior lobe may be distorted by the high vertical pressure.

Reports using rabbits showed that the high SI in the posterior lobe on T1-weighted MR images is associated with the density of secretory granules containing arginine vasopressin (AVP) [15, 16]. In humans, the pituitary posterior lobe shows higher signal intensity than the anterior lobe on T1-weighted MR images from 2 months after birth [23]. In clinical medicine, T1-weighted MR images are used as a diagnostic procedure for diabetes insipidus. The absence of high SI in the pituitary posterior lobe on T1-weighted images indicates that the patients may have central diabetes insipidus [9]. Comparison of the SI ratios of the pituitary posterior lobe between the PDH and control groups demonstrated that the PDH group had a significantly lower SI ratio. We speculate that this significantly lower SI ratio in the PDH group was associated with either a deficit in the axonal transport of AVP produced in the hypothalamus to the pituitary posterior lobe or continuous secretion of AVP from the posterior lobe in response to the high osmolarity due to polyuria [1, 15, 20]. The decrease of SI of the posterior lobe may be a diagnostic marker of PDH dogs.

It is believed that determination of pituitary enlargement by advanced diagnostic imaging systems, such as CT and MRI scans, is highly reliable [6, 14]. However, 80% of the pituitary tumors causing PDH are microadenomas, most of which do not show apparent enlargement even on CT and MRI. Thus, it is often difficult to determine the presence of pituitary tumors by measurement of the size of the pituitary gland. Our results demonstrate that (1) the development of adenoma causes a characteristic displacement of the posterior lobe in a dorsal direction and a low SI ratio for the cerebral cortex and that (2) the level of displacement of the posterior lobe increases according to the level of enlargement. Taken together, these results suggest that assessment of the localization of the posterior lobe within the pituitary gland and determination of SI ratios on T1-weighted MR images are useful for diagnosis of pituitary adenoma.

REFERENCES