Study on MRI Diagnosis f Cerebral diseases in Dogs

犬の脳疾患の MRI 診断に関する研究

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Original Articles

1. Shinji Tamura, Yumiko Tamura, Takeshi Tsuka, Kazuyuki Uchida

Sequential Magnetic Resonance Imaging of an inttracranial hematoma in a dog

Veterinary Radiology and Ultrasound Volume 47 Issue 2 Page 142-146 (2006)

2. Shinji Tamura, Yumiko Tamura, Nobutaka Suzuoka, Aya Ohoka, Takahisa Hasegawa, Kazuyuki Uchida

Multiple metastases of thyroid cancer in the cranium and pituitary gland in two dogs

Journal of Small Animal Practice Volume 48 Issue 4 Page 237-239, April (2007)

3. Shinji Tamura, Yumiko Tamura, Kazuyuki Uchida

Magnetic Resonance Imaging Findings of Neuroaxonal Dystrophy in a Papillon Puppy

Journal of Small Animal Practice Volume 48 Issue 8 Page 458-461, August (2007)

4. Shinji Tamura, Yumiko Tamura, Aya Ohoka, Takahisa Hasegawa, Kazuyuki Uchida

A canine case of skull base meningioma treated with hydroxyurea

The Journal of Veterinary Medical Science Volume 69 Issue 12(2007) in press

Oral Announcement

03/10/13　平成15年度日本小動物獣医学会（中国）

犬の外傷性脳実質内血腫のMRIの経時的変化

田村慎司、田村由美子

03/12/14　第 21 回獣医神経病研究会

犬の外傷性脳実質内血腫の MRI の経時的変化

田村慎司、田村由美子

05/12/11　第 25 回獣医神経病研究会

甲状腺癌が下垂体を含む頭蓋内に多発性転移した犬の 2 例

田村慎司、田村由美子、山本正義、鈴岡宣孝、大岡恵、長谷川孝寿、

内田和幸

06/06/11　第 26 回獣医神経病研究会

神経軸索性ジストロフィーのパピヨンの 1 例

田村慎司、田村由美子、梶谷幸子、梶谷剛、来田千晶、内田和幸

06/12/10　第 27 回獣医神経病研究会

ハイドロキシウレアにより治療した頭蓋内髄膜腫の犬の 1 例

田村慎司、田村由美子、大岡恵、長谷川孝寿、内田和幸

Introduction

Diseases of the cerebral diseases in dogs fall into various categories, including degenerative, metabolic, neoplastic, inflammatory, infectious, idiopathic, iatrogenic, traumatic and vascular disease, and also malformation. They range from diseases such as inter vertebral disk disease, a disease that has been widely recognized since old times and that has relatively well-established pathology and diagnostic and treatment approaches, to those such as necrotizing meningoencephalitis, for which neither the cause nor treatment has been identified. Due to the aging dog population, practicing veterinarians are likely to be faced with cerebral diseases in dogs more frequently than ever before. At the same time, as dog owners become more aware of the quality of veterinary care, they are expecting better treatment of these diseases.

Veterinary magnetic resonance imaging (MRI) was introduced partially in response to such demand in the practice, and since then, antemortem diagnosis of central nervous system (CNS) diseases has improved dramatically. CNS diseases, especially those of the brain, used to be diagnosed using a black box model, based only on the localization of lesions by neurological examinations, and speculation regarding the characteristics of the disease based on factors including signalment, onset pattern and cerebrospinal fluid (CSF) analysis. More detailed diagnosis used to be possible only after necropsy. Introduction of computed tomography (CT) into veterinary medicine permitted the visualization (albeit partial) of intracranial diseases, and introduction of MRI permitted clearer imaging. Because of these advances in diagnostic technology,

along with the aforementioned aging dog population, diseases that were previously thought not to affect so many dogs (e.g. cerebral infarction) actually turned out to be relatively common. Brain tumor also turned out to be a disease that practitioners are frequently faced with. Advances in diagnostic technology also paved the way for causal treatment (e.g. surgical removal of a brain tumor) for CNS diseases that used to be, with some exceptions, treated mainly using symptomatic therapies. In veterinary diagnostic imaging, however, diagnostic criteria for humans are often used, and for diseases such as necrotizing meningoencephalitis and granulomatous meningoencephalitis, for which there are no human counterparts, no diagnostic criteria or other standards exist for humans that can be used for dogs. Thus, there is an urgent need for MRI findings in dogs to be verified via histopathological diagnosis on an ongoing basis. Therefore, for diseases with no previously reported cases of spontaneous onset in dogs, I assessed the clinical symptoms together with the findings from MRI, histopathological studies and various examinations. I present the results of my assessments here, so that they can be used as bases for antemortem diagnosis in the future.

In Chapter 1, I describe the changes that occurred over time in a dog with spontaneously occurring traumatic cerebral intraparenchymal hematoma, at a total of seven observation points from one hour to 14 days after the injury. Histological examination was conducted at autopsy after the dog died on the 14th day of injury. The changes that were seen in MR images were similar to those reported in humans with the same condition. Thus, I obtained data that could be a robust basis for future antemortem MRI diagnosis of intracranial hemorrhage in dogs, including information on the onset

pattern and time elapsing between onset and MRI examination.

In Chapter 2, I describe the MRI characteristics of two canine cases of multiple intracranial (including the pituitary gland) metastases of thyroid carcinoma, and the results of histopathological examination. I also discuss the reasons why there is no previous report of tumor metastases in the canine pituitary gland in the literature based on the clinical symptoms observed in these two cases.

In Chapter 3, I describe a case of neuroaxonal dystrophy in a papillon puppy, which was examined using MRI twice, at three and a half and six months of age. I discuss the changes in the MR images relative to the changes in clinical symptoms. After the puppy was euthanized at six months of age, histopathological examination was also conducted, and herein I also discuss these findings relative to the MRI features.

In Chapter 4, I describe the case of a miniature schnauzer with meningioma in the cranial base, which was treated with hydroxyurea chemotherapy. The efficacy of this treatment regimen was monitored over seven months using MRI.

In all cases summarized in Chapters 1 to 3, the identity of the disease in question could be speculated on based on the signalment, history, and the results of physical, neurological and general laboratory examinations. However, MRI examinations provided information on the localization and/or characteristics of the lesions, and permitted more detailed diagnoses than those possible on the basis of other data. The MRI findings could be verified by a definitive diagnosis made on the basis of histopathological examination. Moreover, for the case described in Chapter 4, MRI was used to monitor the efficacy of chemotherapy, and changes in tumor size over time

during therapy were confirmed. The information on various cerebral diseases in dogs presented here will be useful for the antemortem diagnosis of clinical cases of these diseases and for the monitoring of therapeutic response.

Imaging equipment used was as follows. For the cases described in Chapters 1, 2 and 3, and during the first five months of treatment of the case described in Chapter 4, a 0.2-T MR unit (MRP-20EX; Hitachi Medical, Tokyo, Japan; Fig. 1) was used, and during the seventh month of treatment of the case described in Chapter 4, a 0.3-T MR unit was used (AIRIS2 comfort; Hitachi Medical, Tokyo, Japan; Fig 2). Both were permanent magnet-type MRI systems. For all imaging described here, a quadrature detection coil for the knee joint was used as the surface coil (Fig 3).

The dog described in Chapter 1 was examined while it was immobilized by treatment given for status epilepticus. The other dogs were immobilized by intramuscular injection of 0.02 mg/kg medetomidine hydrochloride and 0.3 mg/kg midazolam followed by intravenous injection of 2-8 mg/kg pentobarbital sodium; these dogs were restrained in the prone position for imaging. Meglumine gadopentetate (0.3 ml/kg; Magnevist; Schering Plough, Kenilworth, NJ, USA) was intravenously injected as a contrast agent as needed.

Figures

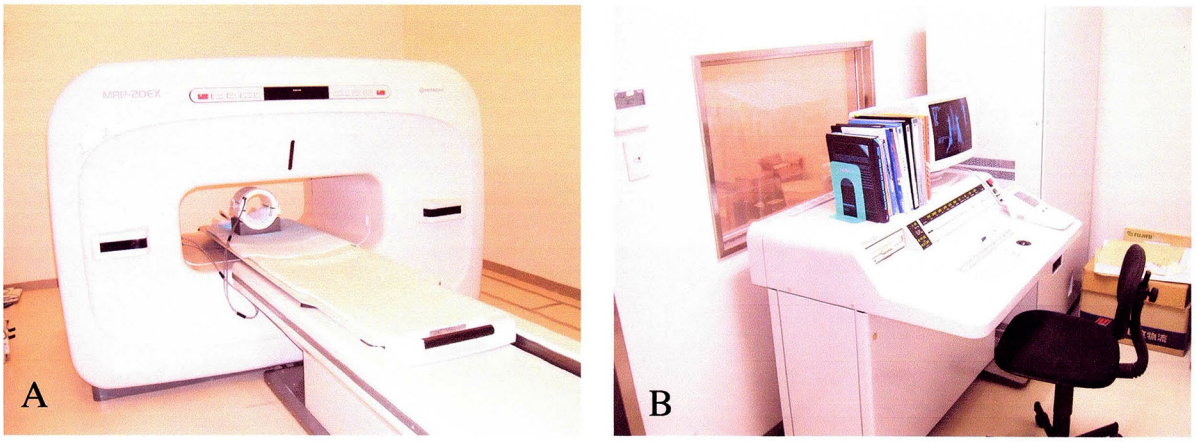

Fig.1: MRP-20EX, Hitachi Medical Co., Tokyo, Japan. 0.2 T permanent magnet system. A: Scan room. Widely opened gantry. B: Control room.

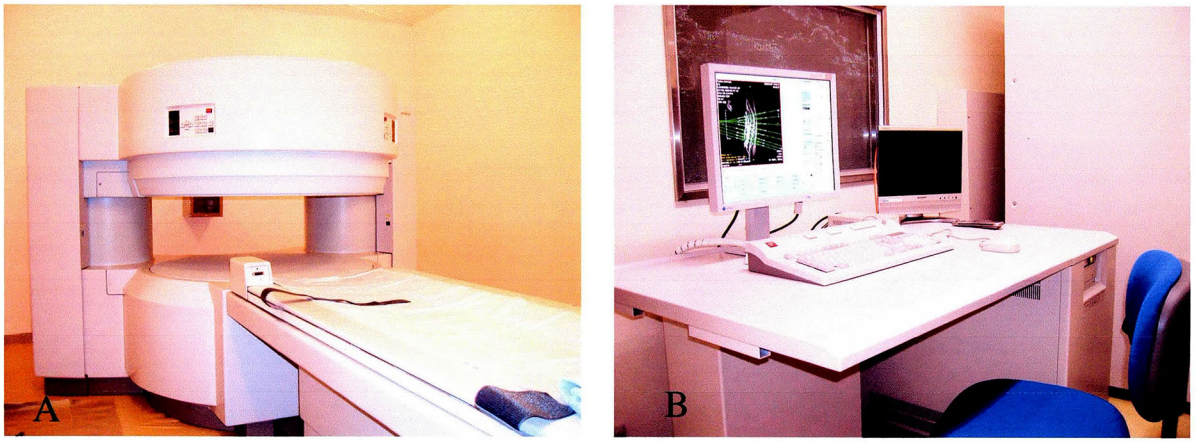

Fig.2: AIRIS II Comfort, Hitachi Medical Co., Tokyo, Japan. 0.3 T permanent magnet system. A: Scan room. Widely opened gantry. B: Control room.

Figures

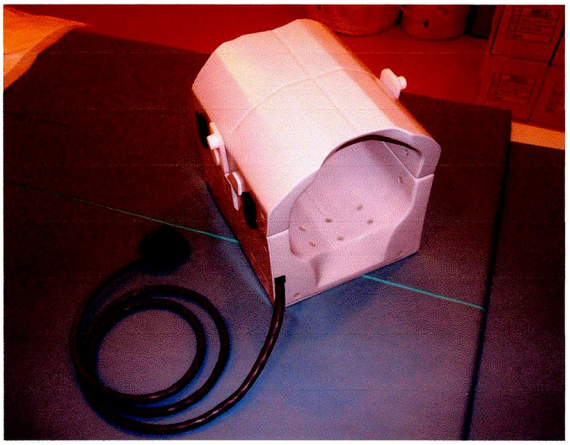

Fig.3: Quadrature detection (QD) coil for human stifle joint of AIRIS II Comfort, Hitachi Medical Co., Tokyo, Japan.

Chapter1

Sequential Magnetic Resonance Imaging of an Intracranial Hematoma in a dog

Abstract

An 8-year-old Yorkshire terrier developed acute onset coma and seizure after cranial trauma. Intracranial hemorrhage was suspected from the clinical signs and history. Low field MR imaging revealed a round mass within the right cerebral hemisphere, compressing the right lateral ventricle and displacing the longitudinal fissure to the left. The lesion was hypointense on T1-weighted images and hyperintense on T2-weighted images, consistent with an acute hemorrhage. MR imaging was performed every 24 h for 6 days from 1 h after the injury, and then on day 14 of hospitalization. With time, the signal intensity changed to hyperintense on T1-weighted images. On T2-weighted images the center of the mass changed to hypointense, and then to hyperintense with a hypointense rim. These changes of signal intensity were related to hemogrobin oxidation.

Case History Report

An 8-year-old female Yorkshire terrier developed continuous circling to the right and excitement soon after falling from a height of 1m. There was right–sided rhinorrhagia and right conjunctival bleeding, as well as changing of consciousness status and absent pupillary light response. Intracranial hemorrhage secondary to cranial trauma was suspected (Braund and others 1994). Immediate intravenous injection of 0.2 mg/kg midazolam hydrochloride succeeded in halting the circling and excitement. 2.0 mg/kg phenobarbital, 6.0 mg/kg pentobarbital, and 2.0 mg/kg dexamethasone were administered to immobilize the dog and prevent of the clinical sign.

Thirty minutes after the injury, MR imaging was performed. Images were obtained with a 0.2 Tesla permanent magnet (MRP-20EX, Hitachi Medical Co., Japan). T1 weighted images (T1WI) were acquired using a repetition time (TR) of 500 ms and an echo delay time (TE) of 20 ms. T2 weighted images (T2WI) were acquired using a TR of 4000 ms and TE of 120 ms. Transverse and dorsal plane images were acquired. The slice thickness was 5 mm, without an interslice gap. There was a mass approximately 20 mm in diameter that formed a well defined globe and was located in the rostroventral part of the right frontal lobe (Figure.1 A, B). The volume of the mass corresponded to 20% of the cross-sectional area. The midline of the brain hemispheres was displaced toward the left. On T1WI the mass was isointense and on T2WI slightly hyperintense to gray matter. The mass did not enhance on T1WI after IV injection of meglumine gadopentetate (0.3ml/kg, Magnevist, Shering Tokyo). The mass was interpreted as a hyperacute intracranial hematoma. Continuous light sedation with antiepileptic drugs

was needed the dog to prevent excitement. To monitor changes in the mass, MR imaging was performed daily while antiepileptic therapy was administered.

On day 2, the mass on T1WI had no change in signal intensity, and on T2WI had become hypointense, centrally. Bleeding was assumed to have stopped because the mass had not enlarged. Glycerin was administered to decrease the intracranial pressure. On day 3, in T1WI the mass was heterogeneously hyperintense(Figure.1 C). In T2WI, there was an increase in size of the hypointense center of the mass(Figure.1 D). On day 5, there was peripheral hyperinteisity in T1WI (Figure. 1 E, F). On T2WI, a hyperintense area of white matter that was thought to be edematous on day 2, worsened from days 3 to 6. On T2WI the cerebral gyri and sulci gradually became unclear from days 2 to 6. The T1WI and T2WI signal intensities of the mass were unchanged on day 6. Treatment with antiepileptics for 6 days and with glycerin for 5 days succeeded in discontinuing sedation without excitement, producing the appearance of reaction to sound and touch on 7 day, and a short period of standing on day 9. However, the dog died suddenly on day 14 because of status epilepticus. In MR examination soon after death, the size of the mass was unchanged, and the mass was now hyperintense at the center and hypointense at the rim on T2WI, but had almost no change on T1WI (Figure. 1 G, H). The edema around the mass was reduced on T2WI. On T2WI the cerebral gyri and sulci were clearly seen. Grossly, the mass extended through most of the right cranial cavity and displaced the midline markedly to the left.

Necropsy was performed on day 14. There was a large hematoma occupying the right hemisphere, from the lateral ventricle to the zona striata. Around the hematoma

there was malacia as well as spongy changes of the neuropil, consisting of Wallerian degeneration of neuronal axons, accumulation of fat-granular cells, and neovascularization. Large numbers of swollen oligodendroglia and atypical astrocytes were distributed diffusely throughout the cerebral parenchyma on both sides of the frontal lobe, the right occipital lobe, and the thalamencephalon. There were ischemic changes in the pyramidal cells scattered widely in the cerebral cortex and hippocampus. In the medulla oblongata, there were a number of swollen oligodendroglia and atypical astrocytes, and the neurons exhibited ischemic necrosis. In the leptomeninges, small numbers of neutrophils and macrophages had accumulated around the blood vessels, and the endothelium of the vessels was hyperplastic. These histologic findings indicated a primary hematoma (Summers and others 1995), with subsequent brain edema and meningitis.

Discussion

Time-related changes on MR images relative to the stage of advancement of hematomas from hyperacute to chronic have been used as criteria for selecting treatment (Bradley 1993, Brooks and others 1989). There are two reports of the MR imaging features of intracranial hemorrhage in animals (Thomas and others 1997, Vernau and others 2002). They describe subacute hematoma associated with cerebral vascular malformation and hemorrhage within an arachnoid cyst. However, time-dependent evaluation of MR imaging patterns has not yet been defined in dogs.

Our applications of sequential MR imaging in a dog with sudden–onset neurologic problems after cranial trauma resulted in the diagnosis of intracranial hematoma and successful recording of the evolving signal intensity of the lesion (Table 1). At the first examination we recognized the intracranial mass to be clearly separate from the brain, both morphologically and in terms of signal intensity. Reports in humans of time-related MR imaging changes of hematomas have shown a progressive chemical reaction of iron ions as components of hemoglobin (Bradley 1993, Brooks and others 1989). It is also known that the features of MR images of hematomas differ according to the strength of the magnetic field (Brooks and others 1989). With a low-field device, increasing of signal intensity on T1WI due to T1 reduction starts earlier than high-field MRI (Brooks and others 1989). The hematoma in our dog was observed with a low–field permanent magnet.

The chemical form of hemoglobin in hyperacute lesions is oxyhemoglobin, which influences the signal intensity similar to that of white matter on T1WI and similar to

fluid on T2WI. In T1WI 24 h after injury, the mass was isointense and in T2WI hypointense, because of the chemical change of oxyhemoglobin to deoxyhemoglobin. The gradual change of deoxyhemoglobin to methemoglobin a few days after injury caused the peripheraly of the mass to become hyperintense on T1WI (Bradley 1993, Brooks and others 1989).

In human studies (Bradley 1993, Brooks and others 1989), time-related changes changing in signal intensity always occur at the edge of the mass and spread toward the center. The signal intensity in T2WI changes from hypointense to hyperintense at 7 to 10 days after injury, with the outflow of methemoglobin from ruptured red blood cells into the mass. The period from 4 to 14 days after injury is called the subacute period, when in T2WI the mass is hypointense for a long interval, because of the accumulation of hemosiderin by macrophage phagocytosis. After 14 days the chronic phase, hemorrhage is absorbed and cyst fluid or a scar replaces the hematoma. The time-related changes in our dog were almost identical with the above changes (Bradley 1993, Brooks and others 1989).

The MRI changes in the brain were the appearance of a hyperintense area around the mass on T2WI at the second to sixth examinations, compression and displacement of the right lateral ventricle, and gradual disappearance of the image of the sulci. The lack of visualization of sulci is caused by increasing intracranial pressure due to secondary white matter edema. In humans, the same MR findings are indicative of brain damage related to edema and intracranial pressure caused by mass (Bradley 1993). In our dog, edema around the hematoma was confirmed on histopathologic examination.

It was interesting to observe the recovery process synchronously with changes in the clinical signs and the MR findings. However, the dog died suddenly on day 14 after injury because of status epilepticus. In response to a request by the owner, the dog was treated at home from day 9 onward. However, the dog had laryngeal paralysis making administration of oral antiepileptic drugs impossible; this is likely why the dog entered status epilepticus.

References

Bradley W. G. Jr. (1993) MR appearance of hemorrhage in the brain, *Radiology* 189, 15–26.

Braund K. G. (1994) Localization using neurological syndromes. In: Clinical Syndromes in Veterinary Neurology 2nd ed London: Mosby,.

Brooks R.A., Di Chiro G., Patronas N. (1989) MR imaging of cerebral hematomas at different field strengths: theory and applications. *J Comput Assist Tomogr* 13, 194-–206.

Summers B. A., Cummings J. F., de Lahunta A. (1995) Injuries to the central nervous system. In: Veterinary Neuropathology, London Mosby.

Thomas W. B., Adams W. H., McGavin M. D., Gompf R. E. (1997) Magnetic resonance imaging appearance of intracranial hemorrhage secondary to cerebral vascular malformation in a dog. *Vet Radiol Ultrasoun* 38 , 371–375.

Vernau KM, LeCouteur RA, Sturges BK, et al. (2002) Intracranial intra-arachnoid cyst with intracystic hemorrhage in two dogs. *Vet Radiol Ultrasoun.* 43 , 449–454.

Figures

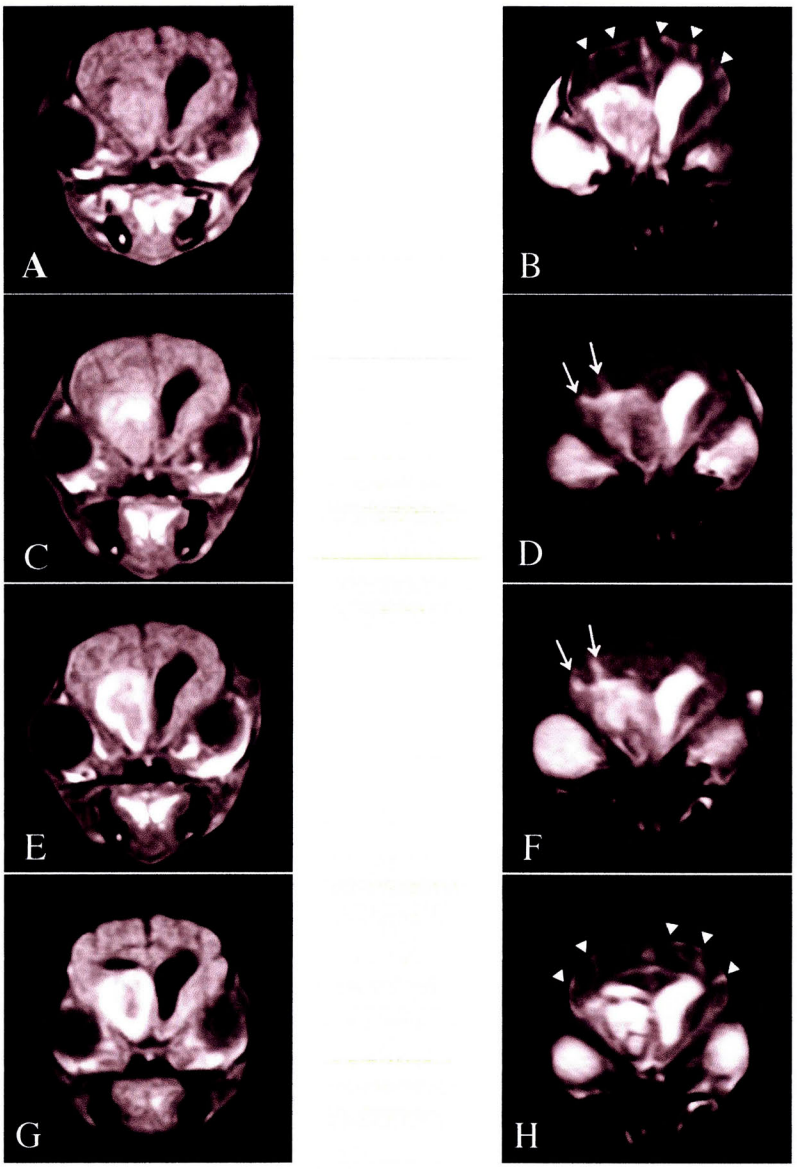

Figure1. Transverse MR images of the brain. There is a large mass in the right frontal lobe. The mass is isointense on T1-weighted images (A) and slightly hyperintense on T2-weighted images (B) 1 h after injury. The signal intensity increases gradually at the edge of the mass on T1-weighted images (C: day 3, E: day 5, G: day 14). T2-weighted images of the mass (D: day 3, F: day 5, H: day 14) show a hypointense area in the center of the mass; on day 14 the mass is hyperintense at the center and hypointense at the rim. The amount of edema around the mass (small arrow) had increased by day 2 and decreased by day 14 on T2-weighted images. The cerebral gyri nad sulci (arrowhead) were indistinct from days 2 to 6 but visible again by day 14.

Table 1. Signal Intensity of Mass, Edema and Sulci of the Cerebrum in The Dog

		Signal Intensity*			
Stage	Time after injury	T1WI	T2WI	Edema	Sulci Conspicuity
Hyperacute	1hr	Iso	Slightly Hyper	Mild	Good
Acute	24hr	Iso	center : Slightly Hypo	Severe	Poor
	3d	Partially Hyper	center : Slightly Hypo	Severe	Poor
Subacute(Early)	4d	Partially Hyper	center : Slightly Hypo	Severe	Poor
	5d	ring shaped Hyper	Mixed Slightly Hypo-Slightly Hyper	Severe	Poor
	6d	ring shaped Hyper	Mixed Slightly Hypo-Slightly Hyper	Severe	Poor
Chronic	14d	ring shaped Hyper	center : hyper, Rim : hypo	Mild	Good

T1WI: T1 weighted image, T2WI: T2 weighted image

* Signal intensity as compared to normal cortical gray matter

Chapter2

Multiple metastases of thyroid cancer in the cranium and pituitary gland in two dogs

Abstract

Two dogs, a 14-year-old female, American Eskimo dog and a 14-year-old male, Maltese dog, were presented with thalamic syndromes, including lowered levels of consciousness, poor postural responses and masses in the neck region. In both dogs, magnetic resonance imaging (MRI) revealed multiple masses inside the cranium, including the pituitary gland. One dog died from status epilepticus two days after MRI and the other died two months after MRI from respiratory failure. These dogs were histopathologically diagnosed with multiple metastases of thyroid cancer occurring inside the cranium, including the pituitary gland. To the authors' knowledge, this is the first time this tumour pattern has been reported in dogs, but it is possible that it is not uncommon.

Introduction

In humans, intracranial metastasis of thyroid cancer is a rare condition representing only 1 per cent of thyroid cancer cases (McWilliams and others 2003). To the authors' knowledge, no canine cases have previously been reported. Metastatic tumours in the pituitary area are also uncommon in humans, accounting for 1 to 26 per cent of pituitary tumours (Bell and others 2001, Simon and others 2004), and in dogs, there is only one previously report of metastatic tumours in the pituitary (a transmissible venereal tumour [Spence and others 1978]). This report describes two canine cases of multiple metastases of thyroid cancer in the cranium, including the pituitary gland.

Case Histories

Case 1

A 14-year-old female, American Eskimo dog was presented with reduced appetite and energy of three weeks' duration, and cluster seizures that had been occurring since the day before.

During a physical examination, masses in the neck and mammary glands, as well as swelling of the mandibular lymph nodes, were found. Neurological examination revealed a lowered level of consciousness and a poor postural response in both hindlimbs and the left forelimb. Serum chemistry findings were normal. Chest radiographs showed a round mass in the cranial lobe of the left lung.

On magnetic resonance imaging (MRI), on both T1- and T2-weighted images, an extraparenchymal mass with the same signal intensity as the surrounding brain parenchyma was seen in the area extending from inside the sella turcica towards the upper part. The image of the mass was enhanced by intravenous administration of 0.3 ml/kg meglumine gadopentetate (Magnevist; Schering Plough). Oedema was noted in the thalamus along the edge of the mass. Another mass was found on the border between the gray and white matter in the left temporal lobe, which was thought to be a metastatic tumour on the basis of its location, its roughly round shape and the severe oedema in the surrounding white matter (Fig 1).

On the basis of these findings, tumours in the pituitary, thyroid and mammary glands, and metastatic tumours in the temporal lobe and lung were suspected. The cluster seizures were treated with phenobarbital and dexamethasone, but the dog died

from status epilepticus two days after MRI examination.

On postmortem examination, a red mass in the temporal lobe and a milky-white mass in the pituitary area were found. Swollen mandibular lymph nodes and many nodules in the lung and spleen were also observed. Histopathologically, the neck mass comprised solid growths of tumour cells with round nuclei varying in size, undergoing active mitosis. The tumours were positive for thyroglobulin and negative for calcitonin and adrenocorticotropic hormone (ACTH) on immunostaining (Fig 2). Similar cells were observed in the other masses. On the basis of these results, the dog was diagnosed with follicular thyroid cancer and systemic metastasis. The difference in the colours of the temporal lobe and pituitary masses was attributed to the differences in blood vessel distribution in the surrounding tissue. The mass in the mammary gland was diagnosed as a benign mixed tumour.

Case 2

A 14-year-old male, Maltese dog was presented with claudication of the left hindlimb and anisocoria. It had had reduced appetite and energy for the past three months, and had been diagnosed with a thyroid tumour and hypothyroidism two months previously, after which the dog had been treated with thyroid hormone.

On physical examination, masses in the neck and swelling of the mandibular lymph nodes were found. Neurologically, lowered levels of consciousness and postural responses in all limbs, as well as anisocoria, were observed. In serum chemistry, an elevated cholesterol level (390.7 mg/dl) and lowered values of T4 and FT4 (6.05 nmol/l

and 0.08 pmol/l, respectively) were found two months before presentation, but after one month of drug therapy the levels mostly returned to normal.

There were no abnormal findings during chest radiography. Masses with similar MRI characteristics as the masses in case 1 were detected in the pituitary area and in the extraparenchymal area in the posterior cranial fossa (Fig 3). MRI suggested that the mass in the neck was located in the left thyroid. On fine-needle aspiration biopsy, scattered masses of cells arranged in a palisading pattern, with ill-defined cell boundaries and nuclei of varying sizes, and a large number of blood components were found.

On the basis of these results, multiple intracranial tumours and thyroid cancer were considered as differential diagnoses. Although the symptoms were treated (including administration of dexamethasone), the dog developed ananastasia one month later and died two months later.

On postmortem examination, other than the masses observed during MRI, a small extraparenchymal tumour was noted in the left pyriform lobe. Histopathological examinations were carried out on the masses in the cranium and neck. In the thyroid mass, tumour cells with clear nucleoli, oval to polygonal-shaped nuclei and weakly acidophilic cytoplasm proliferated densely. Mitosis was found sporadically. The other intracranial masses were comprised of similar tumour cells (Fig 4). These tumour cells were clearly positive for calcitonin. On the basis of these findings, the dog was diagnosed with thyroid C-cell carcinoma and metastases.

Discussion

It is likely that the number of reported cases of intracranial metastasis in cats and dogs is less than those in humans because, in many cases, animals with tumours die or are euthanased before metastasis occurs. The incidence of intracranial metastatic tumours might also have been underestimated because craniotomy is not routinely carried out at postmortem examination in cats and dogs (Bagley 2005). However, the structure of the aortic arch branch in cats and dogs, which is different from that in humans, may prevent intracranial metastasis from occurring readily (Summers and others 1995). Although metastases of thyroid cancer into the cranium or pituitary gland have not been previously reported in dogs, the two cases reported here were encountered within a short period of time. So such metastases might not necessarily be rare conditions.

In case 1, intracranial lesions were strongly indicated by the epileptic seizures caused by the temporal lobe lesion. The lowered levels of consciousness and poor postural responses observed in both cases are symptoms of thalamic syndromes caused by pituitary metastasis and are characteristic of such disorders. However, if a thorough examination is not carried out at the initial presentation, these symptoms may not be linked to intracranial diseases and may be attributed to debility instead. Furthermore, in neither case did any clinical finding suggest an abnormal secretory function of the pituitary gland.

Metastatic tumours in the pituitary area rarely produce clinical symptoms in humans (Ruelle and others 1992). Therefore, it is likely that metastatic tumours in the

pituitary area in dogs have been under-reported because these tumours produce no clear clinical symptoms and tend to be overlooked. In fact, it could be difficult to detect primary pituitary tumours other than those producing ACTH. If lowered levels of consciousness and poor postural response are erroneously interpreted as lethargy and peripheral neuropathy, respectively, they could be confused with the clinical symptoms of hypothyroidism. Therefore, in cases with hypothyroidism caused by thyroid cancer, thyroid preparations alone could be administered without intracranial diseases ever being suspected.

In humans, it is difficult to diagnose metastatic tumours in the pituitary area before surgery (Komninos and others 2004). Endocrine function tests (for example, ACTH-stimulation tests) are useful for differential diagnosis, especially for ACTH-producing tumours. The presence of central diabetes insipidus is the most crucial criterion for the differential diagnosis of pituitary metastatic tumours in humans, because it is found in 1 per cent of cases of pituitary adenoma and in 45.2 per cent of cases of metastatic tumour (Schubiger and Haller 1992). In dogs, however, 10 to 20 per cent of pituitary macroadenoma cases develop pituitary macroadenoma syndrome at, or immediately after, diagnosis (Nelson 1998). As central diabetes insipidus is a component of pituitary macroadenoma syndrome, it is unlikely to be a useful criterion for differential diagnosis in dogs. Dumbbell-shaped tumours extending from the intrasellar to the suprasellar area are likely to be metastatic tumours (Komninos and others 2004). Moreover, the presence of multiple tumours suggests that they are metastatic.

It will be a challenge in the future to develop an approach for the differential diagnosis of canine metastatic tumours in the pituitary area.

References

Bagley, R. S. (2005) Clinical clues to brain tumor. In: Fundamentals of Veterinary Clinical Neurology. Eds R. S. Bagley. Blackwell, Ames. pp 133

Bell, C. D., Kovacs, K., Horvath, E., Smythe, H. & Asa, S. (2001) Papillary carcinoma of thyroid metastatic to the pituitary gland. *Archives of Pathology and Laboratory Medicine* 125, 935-938

Komninos, J., Vlassopoulou, V., Protopapa, D., Korfias, S., Kontogeorgos, G., Sakas, D. E. & Thalassinos, N. C. (2004) Tumors metastatic to the pituitary gland: case report and literature review. *Journal of Clinical Endocrinology and Metabolism* 89, 574-580

McWilliams, R. R., Giannini, C., Hay, I. D., Atkinson, J. L., Stafford, S. L. & Buckner, J. C. (2003) Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years. *Cancer* 98, 356-362

Nelson, R. W. (1998) Endocrine disorders. In: Small Animal Internal Medicine. Eds R. W. Nelson and C. G. Couto. Mosby, St Louis, MO, USA. pp 672-807

Ruelle, A., Palladino, M. & Andrioli, G. C. (1992) Pituitary metastases as presenting lesions of malignancy. *Journal of Neurosurgical Sciences* 36, 51-54

Schubiger, O. & Haller, D. (1992) Metastases to the pituitary--hypothalamic axis. An MR study of 7 symptomatic patients. *Neuroradiology* 34, 131-134

Simon, N., Quyyumi, S. A. & Rothman, J. G. (2004) Follicular thyroid cancer presenting as a sellar mass: case report and review of the literature. *Endocrine*

Practice 10, 62-66

Spence, J. A., Holt, P. E., Sayer, P. D., Rottcher, D. & Cooper, J. E. (1978) Metastasis of a transmissible venereal tumor to the pituitary. *Journal of Small Animal Practice* 19, 175-184

Summers, B. A., Cummings, J. F. & de Lahunta, A. (1995) Metastatic central nervous system tumors. In: Veterinary Neuropathology. Eds B. A. Summers, J. F. Cummings and A. de Lahunta. Mosby, St Louis, MO, USA. pp 391-395

Figures

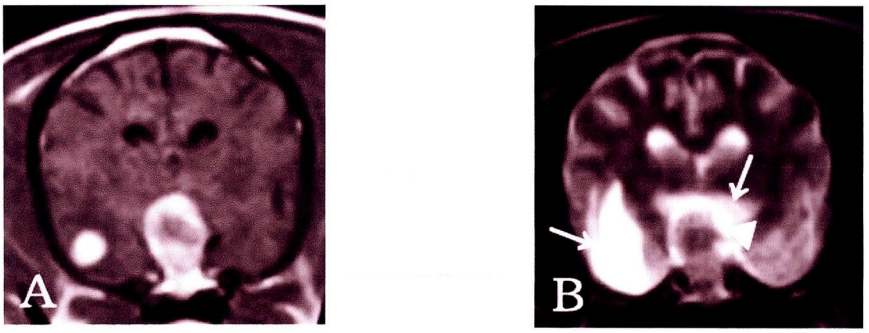

FIG 1. Axial magnetic resonance image of case 1 at the level of the pituitary gland. (A) Post-contrast T1-weighted (T1W) image. Contrast-enhanced tumours can be seen in the pituitary area and in the left temporal lobe. (B) T2-weighted (T2W) image. Oedema can be seen around the tumour (arrow). Cerebrospinal fluid can be seen between the tumour and thalamus, suggesting that it is located outside the brain parenchyma (arrowhead)

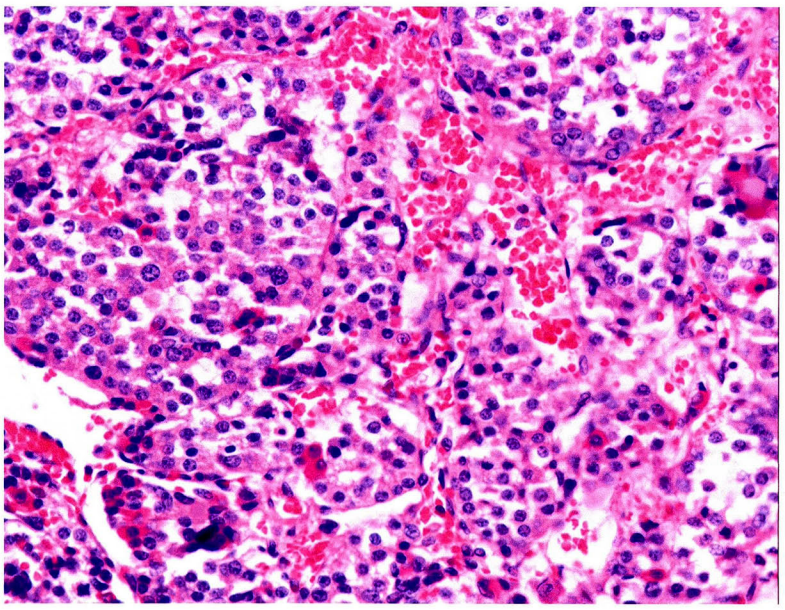

FIG 2. Photomicrograph of the tumour in the pituitary area in case 1. Tumour cells derived from thyroid follicular cells form a solid growth, which is split into honeycomb-like components by fine-grained connective tissue, and appears to replace the normal cells. Capillaries are growing in the stroma. Haematoxylin and eosin (H&E). ×400

Figures

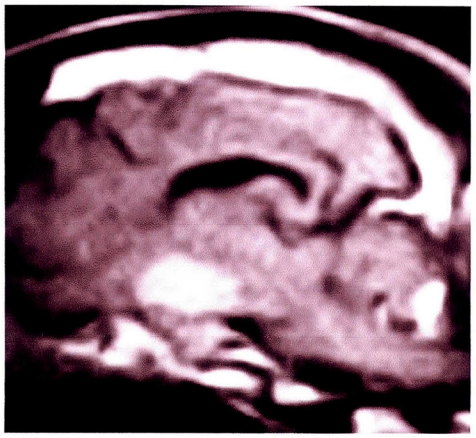

FIG 3. MRI post-contrast T1W paramedian sagittal image of case 2. Contrast-enhanced tumours can be seen in the pituitary area and in the extraparenchymal area of the posterior cranial fossa

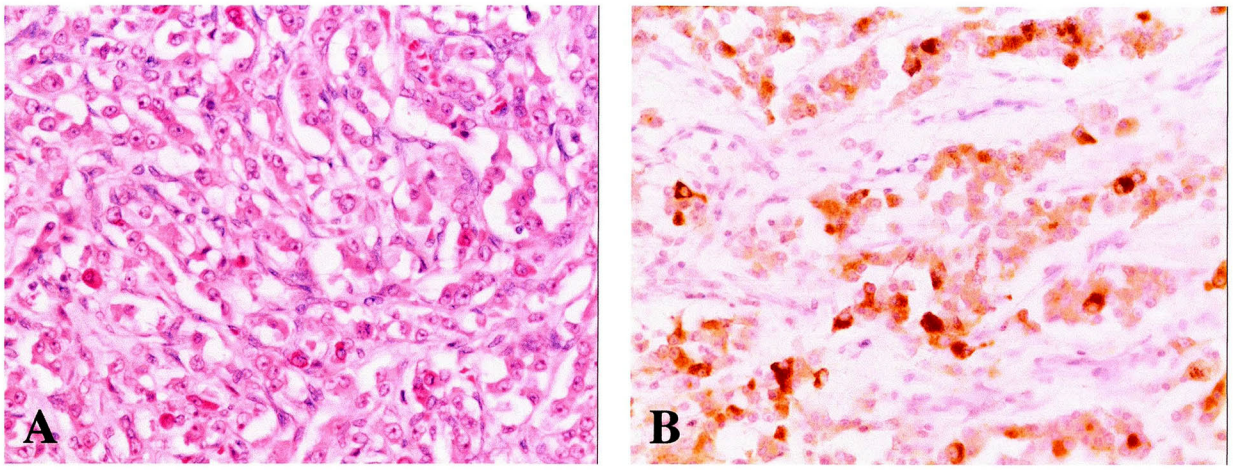

FIG 4. Photomicrographs of the tumour in the pituitary area in case 2. (A) Tumour cells similar to those in the thyroid show irregular glandular-cavity-like proliferation. In the stroma, infiltration of inflammatory cells consisting mainly of neutrophils is obvious, and a slight increase in microglial cell number and vascular endothelial proliferation can be seen in the surrounding area. H&E. ×400. (B) Calcitonin-stained section. Cells are clearly positive for calcitonin. ×400

Chapter3

Magnetic Resonance Imaging Findings of Neuroaxonal Dystrophy in a Papillon Puppy

Abstract

A 3.5-month-old papillon puppy was brought to our clinic with chief complaints of progressive quadriparesis, ataxia and head tremor. Lesions in the cerebellum, brain stem and spinal cord were suspected on the basis of a neurological examination. No abnormality was found in a clinicopathological examination or on MRI. Among differential diagnosis, an inflammatory disease, a degenerative condition or a storage disorder were considered on the basis of these results. After this time, the initial symptoms progressed, and glossoplegia and dysphagia developed at 6 months of age. At a second MRI, severe atrophy of the entire brain was found. After these examinations, the puppy was euthanized and histopathologically diagnosed with neuroaxonal dystrophy. Because MRI detected abnormal features that were characteristic of neuroaxonal dystrophy in this case, we speculate that MRI can assist in the premortem diagnosis of this disease.

Introduction

Neuroaxonal dystrophy is a degenerative disease of the central nervous system that is characterized by the degeneration of neurons and axons. Cases in dogs, cats, rats, sheep, horses and humans have been described in the literature (Franklin and others 1995). Canine cases have been reported, though sporadically, in several breeds (Cork and others 1983), including rottweilers (Chrisman and others 1984, Bennett and others 1997, Evans and others 1988, Siso and others 2001), Chihuahuas (Blakemore and others 1985), collie sheep dogs (Clark and others 1982), Jack Russell terriers (Sacre and others 1993) and English cocker spaniels (McLellan and others 2003). There is also a report of neuroaxonal dystrophy in all members of a litter of five papillon puppies, in which the clinical course and histopathological features of the disease are described in detail (Franklin and others 1995). According to the report of Franklin and colleagues, progressive ataxia, hypermetria and reduced postural reaction of the limbs were observed, and axonal degeneration was found histopathologically in both the white and gray matter. However, at present, there is no known method for premortem diagnosis of neuroaxonal dystrophy. We report here another case of neuroaxonal dystrophy in a papillon puppy, for which we describe MRI changes over time, in addition to describing a clinical course and histopathological features that are similar to those of the cases reported by Franklin and colleagues.

Case History

A 3.5-month-old female papillon, weighing 1.1 kg, was referred to our clinic for the evaluation of progressive neurologic abnormalities including tetraparesis, ataxia and head tremor, which were first observed at 2 months of age. The puppy had been born a singleton. The puppy could not stand, but adopt a prone position. Voluntary movements were observed in the upper body, and hypermetria was observed in the forelimbs. Both hind limbs tended to be extended. There was no impairment of consciousness. A neurological examination at the initial presentation showed reduced postural reaction of the limbs, lack of blink response to menace, and head tremor, which was aggravated by excitation and disappeared when at rest. Urination was involuntary and could be easily induced by applying pressure manually. At that time lesions in the cerebellum, brain stem and spinal cord were suspected. No abnormality was found in a complete blood count, or a biochemical examination. Among differential diagnosis in a young animal with progressive multifocal signs, an inflammatory disease, a degenerative condition or a storage disorder were considered on the basis of these findings, but leukocyte deformation, which indicates a storage disease, was not observed. Head MRI was performed using a 0.2-T system (MRP-20EX, Hitachi Medical Corporation, Tokyo). T1-weighted images were acquired using a repetition time of 500 ms and an echo delay time of 20 ms. T2-weighted images were acquired using a repetition time of 4000 ms and an echo delay time of 120 ms. Transverse, dorsal and sagittal plane images were acquired. The slice thickness was 5 mm, and there was no interslice gap. No contrast medium was used. No clear abnormality was found in

either T2- or T1-weighed images (Fig.1).

The puppy was not treated for the condition, and head tremor, hypermetria, and extension of the hind limbs became gradually aggravated, and generalized amyotrophy progressed. At 6 months of age, the puppy's level of consciousness decreased, it was tetraplegic with increased tone in all four limbs and even the tail, and the hind limbs could not be bent manually; therefore, the patellar reflex could not be examined. Dysphagia prevented the puppy from taking any food. Algesthesia of the limbs was normal (Fig.2). Complete blood count and biochemical examination results at this time were normal. A second head MRI showed clearly delineated cerebral sulci and enlarged lateral ventricles, indicating severe atrophy of the cerebrum. In a sagittal image, atrophy was also observed in the interthalamic adhesion, cerebellum, mesencephalon, pons and medulla oblongata, and the fourth ventricle was enlarged. The arbor vitae of the cerebellum was less clear relative to its appearance at initial presentation (Fig.3). In a cerebrospinal fluid sample obtained via a cisternal tap, the cell count was normal (<2/μl) and protein levels were slightly lowered (6.0 mg/dl; reference value 8.0-30.0 mg/dl). The level of Ig-G antibody against canine distemper virus measured by the immunoperoxidase method was 5120-fold for serum and less than 5-fold for cerebrospinal fluid, indicating no infection with this virus. After these examinations, the puppy was euthanized for humane reasons.

In a pathological autopsy, mild atrophy of the cerebellum was observed (Fig.4). A histopathological examination detected small intracellular vacuoles diffusely present and reactive astrocytes diffusely proliferating in the white matter of the whole

central nervous system. There was no substantial change in the cortex. In the cerebellum, degeneration and enlargement of many axons was observed, especially in the fastigial nucleus, interpositus nucleus and dentate nucleus. In the cortex, a small number of Purkinje cells were lost or had degenerated, and a moderate number of torpedoes were sporadically found in the granular layer. In the medulla oblongata, loss and degeneration of neurons in the olivary nuclei and a large number of small spheroids were observed. In the spinal cord, vacuoles were present diffusely, mainly in the white matter. In the dorsal horn, neurons were decreased in number and many axons had degenerated and become enlarged. In the ventral horn, motor neurons were mostly normal. Normal structures were maintained in the femoral and sciatic nerves (Fig.5). On the basis of these findings, the puppy was diagnosed with neuroaxonal dystrophy.

Discussion

Based on the histopathological examination, we speculated that the loss of blink response to menace and head tremor observed in this puppy were clinical symptoms caused by a disorder of the cerebellum. We considered that the impairment of consciousness that appeared concurrently with the progression of the other symptoms was a clinical manifestation of an impaired reticular activating system, that the glossoplegia and dysphagia were manifestations of a functional disorder of the medulla oblongata, and that the spastic quadriparesis was a manifestation of disordered upper motor neurons due to impaired white matter tracts in brain stem and spinal cord. As was also reported by Franklin and others (1995), in the present case the patellar reflex was normal at the age of 19 weeks, but we could not examine the reflex at the age of 6 months because of the rigidity of the puppy's knee joints.

In our case, the neurological findings at first presentation mainly suggested dysfunction of the cerebellum, brain stem and spinal cord. In addition, a degenerative disease was suspected because of the chronic progressive cerebellar manifestation that developed from 2 months of age. The clinical symptoms and histopathological changes were very similar to those reported by Franklin and colleagues (1995). In our case, the puppy did not have any littermates, so we cannot comment on whether entire litters tend to have the same disease, as was observed in a previous instance. In our case, as for the puppies described by Franklin and colleagues, the cause of the disease was not known.

A hyperintense cerebellum on T2-weighted MR and fluid-attenuated inversion recovery (FLAIR) images, and an elevated cerebellar diffusion pattern on

MRI are characteristic of neuroaxonal dystrophy in humans (Sener 2004). In human cases, the most characteristic microscopic feature is cerebellar atrophy. In the present case, a hyperintense cerebellum was not observed on T2-weighted MR images, and FLAIR and diffusion-weighted images could not be acquired with our MRI system.

There have been several reports describing the MRI findings for canine cases of degenerative diseases of the central nervous system, including storage diseases. These have tended to comprise atrophy of the central nervous tissue and bilateral high signal lesions in T2-weighted MR images (Kaye and others 1992, Cozzi and others 1998, Mariani and others 2001, Merwe and others 2001, Koie and others 2004, Garosi and others 2005, Matsuki and others 2005). In these degenerative diseases, the degree of atrophy observed in the MR images and the MR signal intensity in the lesions would be expected to change depending on factors including the progression of degeneration in the nervous tissue, the substances accumulated in the lysosomes and the degree of calcification. Lesions for which degeneration has progressed tend to appear with high signal intensity on T2-weighted MR images and low signal intensity on T1-weighted MR images, whereas when calcification occurs, low signal intensity is seen in both sequences. In the present case, progressive atrophy in the cerebrum, cerebellum and brain stem was found on MRI. MR images obtained at the age of 3.5 months were normal, suggesting that unable to detect MR changes in an early stage. Appearance of major lesions in the second study, suggesting reinforcing the hypothesis of a progressive disorder, and observation of diffuse atrophy, again reinforcing the hypothesis of a degenerative disease and evident in a late stage of this animal's disease. Post-contrast

images were not acquired in the present study, but would be necessary in order to distinguish neuroaxonal dystrophy from other conditions, including inflammatory lesions.

In the present case, the imaging findings were consistent with the lesions found histopathologically. Spinal cord MRI was not performed in the present case, but we speculate that abnormality would have been detected given the observed histopathological changes. Repeated MRI studies of brain and spinal cord in these animals, corresponding to different stages of the disease would be useful for the antemortem diagnosis of neuroaxonal dystrophy in papillons, in association with other factors including breed, age of onset and clinical symptoms.

References

Bennett, P. F. & Clarke, R. E. (1997) Laryngeal paralysis in a rottweiler with neuroaxonal dystrophy. *Australian Veterinary Journal* **75**, 784-786

Blakemore, W. F. & Palmer, A. C. (1985) Nervous disease in the chihuahua characterised by axonal swellings. *Veterinary Record* **117**, 498-499

Chrisman, C. L., Cork, L. C. & Gamble, D. A. (1984) Neuroaxonal dystrophy of Rottweiler dogs. *Journal of the American Veterinary Medical Association* **184**, 464-467

Clark, R. G., Hartley, W. J., Burgess, G. S., Cameron, J. S. & Mitchell G. (1982) Suspected inherited cerebellar neuroaxonal dystrophy in collie sheep dogs. *New Zealand Veterinary Journal* **30**, 102-103

Cork, L. C., Troncoso, J. C., Price, D. L., Stanley, E. F. & Griffin, J. W. (1983) Canine neuroaxonal dystrophy. *Journal of Neuropathology and Experimental Neurology* **42**, 286-296

Cozzi, F., Vite, C. H., Wenger, D. A., Victoria, T, & Haskins, M. E. (1998) MRI and electrophysiological abnormalities in a case of canine globoid cell leucodystrophy. *Journal of Small Animal Practice* **39**, 401-405

Evans, M. G., Mullaney, T. P. & Lowrie, C. T. (1988) Neuroaxonal dystrophy in a rottweiler pup. *Journal of the American Veterinary Medical Association* **192**, 1560-1562

Franklin, R. J., Jeffery, N. D. & Ramsey, I. K. (1995) Neuroaxonal dystrophy in a litter of papillon pups. *Journal of Small Animal Practice* **36**, 441-444

Garosi, L. S., Penderis, J., McConnell, J. F. & Jakobs, C. (2005) L-2-hydroxyglutaric aciduria in a West Highland white terrier. *Veterinary Record* **156**, 145-147

Kaye, E. M., Alroy, J., Raghavan, S. S., Schwarting, G. A., Adelman, L. S., Runge, V., Gelblum, D., Thalhammer, J. G. & Zuniga, G. (1992) Dysmyelinogenesis in animal model of GM1 gangliosidosis. *Pediatric Neurology* **8**, 255-261

Koie, H., Shibuya, H., Sato, T., Sato, A., Nawa, K., Nawa, Y., Kitagawa, M., Sakai, M., Takahashi, T., Yamaya, Y., Yamato, O., Watari, T. & Tokuriki, M. (2004) Magnetic resonance imaging of neuronal ceroid lipofuscinosis in a border collie. *Journal of Veterinary Medical Science* **66**, 1453-1456

Mariani, C. L., Clemmons, R. M., Graham, J. P., Phillips, L. A. & Chrisman, C. L. (2001) Magnetic resonance imaging of spongy degeneration of the central nervous system in a Labrador Retriever. *Veterinary Radiology and Ultrasound* **42**, 285-290

Matsuki, N., Yamato, O., Kusuda, M., Maede, Y., Tsujimoto, H. & Ono, K. (2005) Magnetic resonance imaging of GM2-gangliosidosis in a golden retriever. *Canadian Veterinary Journal* **46**, 275-278

McLellan, G. J., Cappello, R., Mayhew, I. G., Elks, R., Lybaert, P., Watte, C. & Bedford, P. G. (2003) Clinical and pathological observations in English cocker spaniels with primary metabolic vitamin E deficiency and retinal pigment epithelial dystrophy. *Veterinary Record* **153**, 287-292

Sacre, B. J., Cummings, J. F. & De Lahunta, A. (1993) Neuroaxonal dystrophy in a Jack Russell terrier pup resembling human infantile neuroaxonal dystrophy. *The Cornell Veterinarian* **83**, 133-142

Sener, R. N. (2004) Diffusion-weighted and conventional MR imaging findings of neuroaxonal dystrophy. *American Journal of Neuroradiology* **25**, 1269-1273

Siso, S., Ferrer, I. & Pumarola, M. (2001) Juvenile neuroaxonal dystrophy in a Rottweiler: accumulation of synaptic proteins in dystrophic axons. *Acta Neuropathologica* **102**, 501-504

van der Merwe, L. L. & Lane, E. (2001) Diagnosis of cerebellar cortical degeneration in a Scottish terrier using magnetic resonance imaging. *Journal of Small Animal Practice* **42**, 409-412

Figures

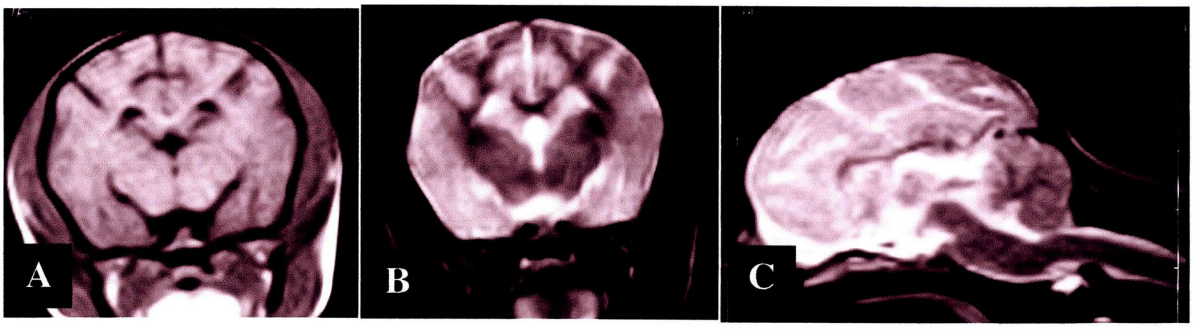

Fig.1. MR images at initial presentation (at 3.5 months of age). (A) T2-weighted and (B) T1-weighted transverse images at the level of the thalamus. (C) T2-weighted median sagittal image. There was no clear abnormality in either the T2- or T1-weighted images.

Fig.2. Appearance of the puppy at 6 months of age. Spastic quadriparesis was observed.

Figures

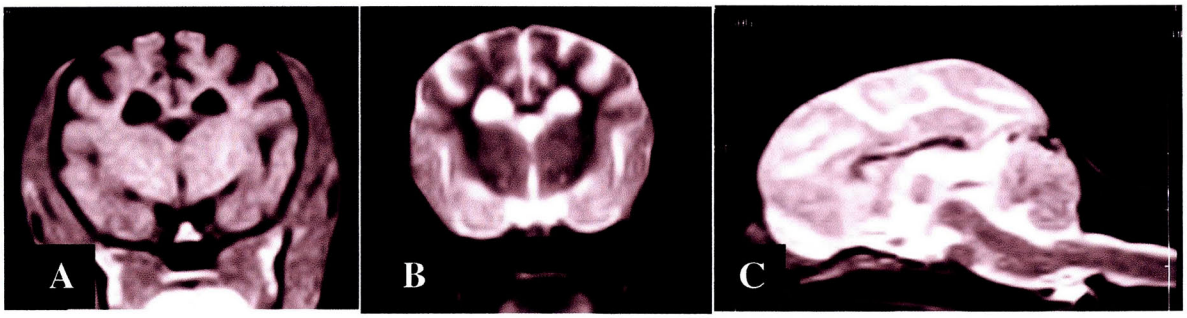

Fig.3. MR images obtained at 6 months of age. (A) T2-weighted and (B) T1-weighted transverse images at the level of the thalamus. Cerebral atrophy was observed. (C) T2-weighted median sagittal image. The cerebellum and brain stem were atrophied, and the arbor vitae of the cerebellum was less clear relative to its appearance at initial presentation.

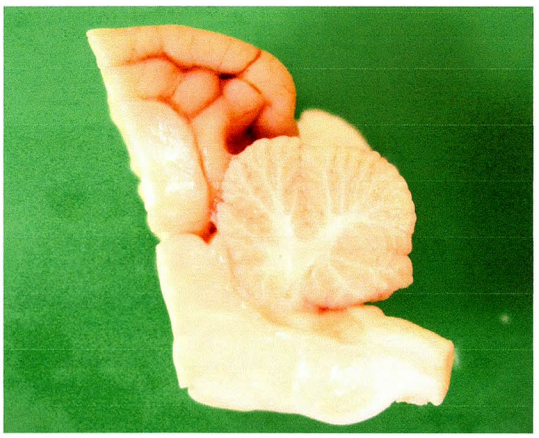

Fig.4. Sagittal cut section of the fixed cerebellum. Mild atrophy of the cerebellum was observed.

Figures

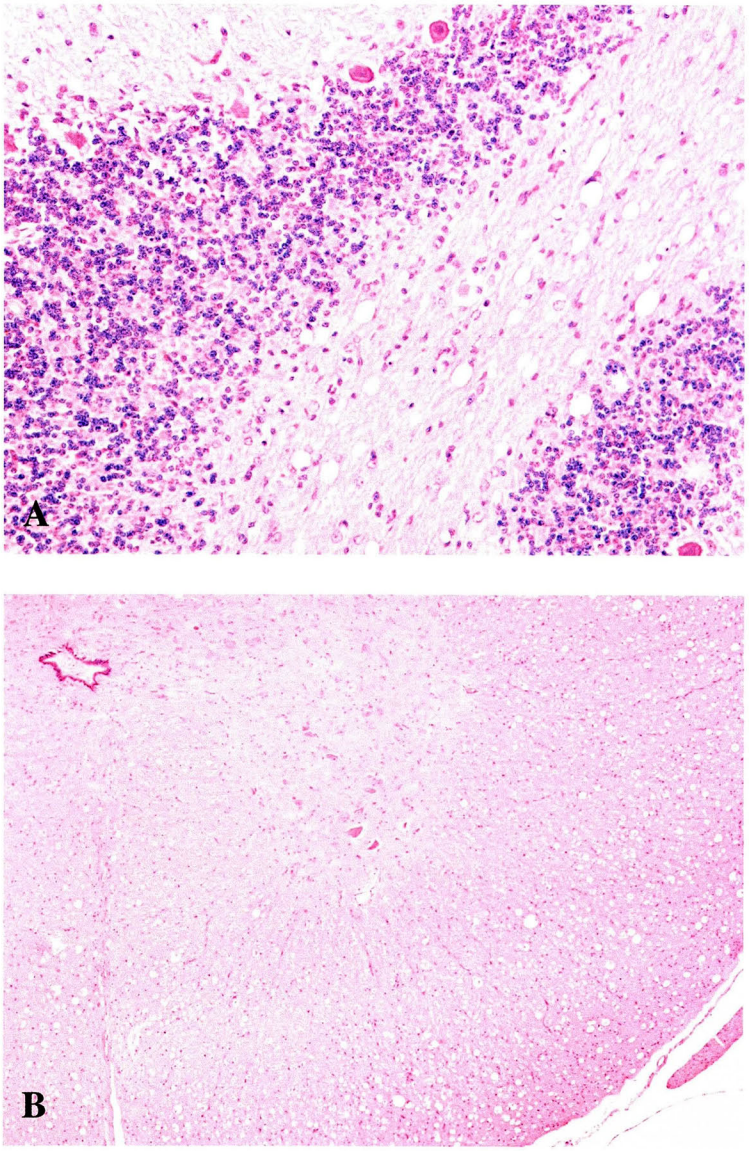

Fig.5. Photomicrographs of histopathological specimens. (A) Cerebellum. In the white matter, axonal vacuolar degeneration was observed to a large extent and reactive astrocytes were proliferating diffusely. In the cortex, a small number of Purkinje cells had been lost or had degenerated, and torpedoes were sporadically found in the granular layer. Hematoxylin and eosin, ×200. (B) Cross-section of spinal cord white matter. Vacuolation of axons ranging in size from small to large was observed diffusely throughout the white matter. Hematoxylin and eosin, × 40.

Chapter4

A Canine Case of Skull Base Meningioma Treated with Hydroxyurea

Abstract

An 11-year-old female miniature schnauzer was tentatively diagnosed with the skull base meningioma, based on several examinations. Because surgical treatment was difficult, and outpatient radiation therapy was not available in the local area, chemotherapy with hydroxyurea combined with dexamethasone was selected. The patient's clinical symptoms improved after one week of treatment, and the tumor size was obviously reduced on MRI performed 37 days after treatment began. The patient received hydroxyurea for 7 months, with symptoms remaining stable, and the tumor re-increased to almost the same size at 7 months as that at the initial examination. At that time, hydroxyurea was discontinued. The patient died from pulmonary edema 14 months after treatment began. Pathologically, the tumor was diagnosed as a meningioma.

Introduction

In dogs, unlike in humans and cats, intracranial meningioma is likely to infiltrate the surrounding tissues, making radical resection of the tumor difficult [10]. Although a combination of surgery and radiation therapy has been shown most effective for treatment of the disease, surgical intervention is sometimes more difficult in dogs than in humans, depending on the affected site, because the temporal muscles of dogs are much thicker than those of humans [1, 2]. Few veterinary hospitals provide radiation therapy for tumors, which requires anesthesia to be administered multiple times during the course of treatment. Therefore, veterinarians treating dogs with intracranial meningioma need other treatment options. We report a canine case of inoperable meningioma in the skull base that was treated with hydroxyurea, which has been used to treat human meningiomas [7, 8]. Hydroxyurea chemotherapy was combined with steroid treatment, resulting in reduced tumor size and improved clinical symptoms..

Case History

An 11-year-old female miniature schnauzer presented with a four-to-five-month history of progressive impairment of vision and hearing. On physical examination, bradycardia was observed. A neurological examination revealed a decreased level of consciousness, loss of pupillary light reflex, absence of menace response, and slightly reduced postural reactions in all limbs. No abnormalities were found with respect to hematology or blood chemistry, or in thoracic and abdominal X-ray examinations. Magnetic resonance imaging (MRI) of the brain (0.2T MRP20-EX; Hitachi Medico, Tokyo, Japan) revealed a mass in the extraparenchymal area spreading from the sella turcica to the right olfactory bulb, which was hypointense on T1-weighted images (T1WIs), hyperintense on T2-weighted images (T2WIs), uniformly strongly enhancing upon intravenous administration of 0.3 ml/kg meglumine gadopentetate (Magnevist; Schering Plough), and had a dural tail sign. Mid-sagittal plane images showed that the thalamus and midbrain were dislocated to the dorsocaudal side by the mass effect. Edema was also observed around the mass (Fig. 1). We compared changes in tumor size over time, using the maximum width and height (excluding the dural tail), on transverse MRI images at the pituitary level. Initially, the tumor was 14.2 mm × 10.3 mm in size (width × height). Meningioma in the skull base was suspected, but surgical excision was considered difficult because of the location and size of the tumor. We offered the patient's owner several treatment options, including radiation therapy, chemotherapy, symptomatic treatment with steroids, and any combination of these options. After discussion, we decided to administer hydroxyurea chemotherapy combined with

symptomatic treatment with a steroid.

Initially, 30 mg/kg hydroxyurea was administered orally three times a week, plus 0.5 mg/day oral dexamethasone to treat the edema around the tumor. A complete blood count (CBC) was obtained every two weeks to detect any myelosuppression in response to hydroxyurea treatment. One week after treatment began, the dog's vision and hearing recovered, and the level of consciousness returned to normal. On MRI performed at 37 days after treatment began, the tumor was smaller and the surrounding edema had disappeared. At that time, the tumor was 9.5 mm × 9.1 mm in size (Fig. 2). Dexamethasone was tapered, and mild worsening of the neurological symptoms, particularly the visual and auditory ones, was observed at times. The symptoms were controlled by an increase in the dexamethasone dose. Five months after treatment began, loss of vision and depression developed. At that time, the tumor was 9.8 mm × 9.5 mm in size, with no edema (Fig. 2), and the dexamethasone dose was 0.5 mg/day. Increasing the hydroxyurea dose to 45 mg/kg three times a week with no change to the dexamethasone dose relieved these symptoms. Packed cell volume (PCV) gradually decreased during the course of treatment, which was possibly caused by the hydroxyurea. At 7 months after the initial presentation, when the PCV had decreased to 36% (from 48% at the initial presentation), hydroxyurea was discontinued. At that time, the dexamethasone dose was 0.25 mg/day. On MRI carried out at the same time as the PCV measurement (0.3T AIRIS2 Comfort; Hitachi Medico, Tokyo), the tumor was 14.0 mm × 11.4 mm in size, without edema (Fig. 2). One month after discontinuation of hydroxyurea treatment, the PCV fluctuated around 40%. Neutropenia was not observed

at any time during treatment. Two months after treatment began, hepatomegaly and elevated hepatic enzyme levels were noted. Although these symptoms were considered to be related to dexamethasone, it was difficult to determine the appropriate time at which to discontinue the drug. At around 11 months after the first presentation, signs of Cushing's syndrome began to appear, and at 14 months, the patient died at her owner's home from pulmonary edema of unknown cause. On post-mortem MRI, no definitive evaluation was possible because contrast media could not be used, although the tumor was seen to be enlarged on several T2WIs relative to images obtained at 7 months.

At necropsy, a large extramedullary mass, 15.2mm x 12.2mm in diameter, white to red in color, was found on the ventral surface of the brain. Histopathological examinations revealed that the mass consisited of solid proliferation of ovoid to spindle-shaped tumor cells, sometimes forming whorl structures and a few psammoma bodies. In the stroma, there were mild neutrophilic infiltration and cholesterol deposits. Based on these findings, the tumor was diagnosed as meningioma, meningothelial type (Fig. 3). Based on findings including systemic calcinosis (in the lungs, kidneys, spleen, liver, and cerebrovascular vessels), severe vacuolar degeneration of hepatic cells, and atrophy of the adrenal cortex, we determined that the patient had eventually developed iatrogenic Cushing's syndrome. Apart from these changes, pulmonary congestive edema was also obserbed.

Discussion

Hydroxyurea is an antimetabolite that specifically affects the S stage of the cell cycle [4]. Hydroxyurea can be used for years with acceptable and reversible toxicity in humans, and for this reason it may be the optimal drug for treating slow-growing tumors with low mitotic indices, such as unresectable and recurrent meningioma, despite the controversy over its efficacy [4]. In dogs, hydroxyurea is used for the treatment of chronic lymphocytic leukemia (CLL) [6], polycythemia [9], and essential thrombocythemia [3]. Lomustine and carmustine, which pass through the blood-brain barrier and are used for certain human brain tumors, are not effective treatments for canine meningioma [1]. A previous case report described a dog with meningioma that survived for 13 months on lomustine and prednisolone [5], although no data on tumor size after treatment were provided. For these reasons we selected hydroxyurea to treat the present case.

In the present case, the cytostatic and tumor-shrinking effects of hydroxyurea in combination with the antiedema effect of dexamethasone appeared to result in symptom relief. Specifically, when symptoms worsened after 5 months of treatment, the hydroxyurea dose was increased, resulting in suppression of tumor growth and reduction in tumor size. After a discussion about treatment with the owner, hydroxyurea chemotherapy was started at a low dose of 30 mg/kg, based on the therapeutic dose range used for dogs with CLL. One of the side effects of hydroxyurea is progressive myelosuppression, which can be attenuated before it becomes severe by temporarily decreasing the dose or discontinuing the medication when neutropenia is detected

during routine CBC monitoring [6]. We discontinued hydroxyurea treatment because of a persistent decrease in PCV, although neutropenia did not occur in this case. It is unclear whether the gradual decrease in PCV was due to hydroxyurea-induced myelosuppression, or in fact whether discontinuation of treatment was appropriate. Although hydroxyurea is used at a dose of 30-50 mg/kg in dogs with CLL, further investigation of the optimal dose range for treating canine meningiomas is necessary.

In the present case, symptomatic treatment with dexamethasone eventually induced iatrogenic Cushing's syndrome. When using steroids, matters warranting consideration are selection of steroids, temporary use of steroids only when clinical symptoms worsen, and combined use with other antiedema agents such as acetazolamide.

In a review of the treatment outcomes for intracranial meningioma in dogs, it was found that the median survival time was approximately 3.9 months with symptomatic treatment with steroids alone, 7 months with surgery alone, and 16.5 months with surgery and radiation therapy [1]. In that analysis, however, the location of the tumor, the tumor size at diagnosis, the histological type of the tumor, and the patient's age were not taken into consideration. Therefore, although our patient survived for 14 months with chemotherapy combined with a steroid, care should be taken when comparing her survival time with those of other reported cases. In the present case, more important is the fact that the combination of steroid and hydroxyurea chemotherapy reduced the tumor size, which suggests that this combination therapy may be an effective approach for treating meningiomas in dogs. Multimodal therapies combining chemotherapy with

surgery or radiation therapy can also be considered. There is little information available in the literature about chemotherapy for canine brain tumors, including meningiomas, and the matter has not yet been extensively investigated [1]. More hydroxyurea-treated cases of canine meningioma should be studied in order to further investigate the optimal dosage and efficacy of this chemotherapeutic agent.

References

1. Adamo, P. F., Forrest, L. and Dubielzig, R. 2004. Canine and feline meningiomas: Diagnosis, treatment, and Prognosis, *Compend. Contin. Educat. Pract. Vet.* 26: 951-960.
2. Bagley, R. S. 2005. pp.303-322. Treatment of important and common diseases involving the intracranial nervous system of dogs and cats. *In*: Fundamentals of Veterinary Clinical Neurology. (Bagley R. S. ed), Blackwell Publishing Ltd, Ames, IA, U.S.A.
3. Bass, M. C. and Schultze, A. E. 1998. Essential thrombocythemia in a dog: case report and literature review. *J. Am. Anim. Hosp. Assoc.* 34: 197-203.
4. Hoshino, T., Nagashima, T., Murovic, J. A., Wilson, C. B., Davis, R. L. 1986 Proliferative potential of human meningiomas of the brain. A cell kinetics study with bromodeoxyuridine. *Cancer* 58:1466-1472.
5. Jung, D. I., Kim, H. J., Park, C., Kim, J. W., Kang, B. T., Lim, C. Y., Park, E. H., Sur, J. H., Seo, M. H., Hahm, D. H. and Park, H. M. 2006. Long-term chemotherapy with lomustine of intracranial meningioma occurring in a miniature schnauzer. *J. Vet. Med. Sci.* 68: 383-386.
6. Leifer, C. E., Matus, R. E., Patnaik, A. K. and MacEwen, E. G. 1983. Chronic myelogenous leukemia in the dog. *J. Am. Vet. Med. Assoc.* 183: 686-689.
7. Chamberlain, M.C. 2004. Intracranial meningiomas, *Curr. Treat. Opin. Neurol.* 6: 297-305.
8. Mason, W. P., Gentili, F., Macdonald, D. R., Hariharan, S., Cruz, C. R. and Abrey,

L.E. 2002. Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma. *J. Neurosurg.* 97: 341-346.

9. Moore, K. W. and Stepien, R. L. 2001. Hydroxyurea for treatment of polycythemia secondary to right-to-left shunting patent ductus arteriosus in 4 dogs. *J. Vet. Intern. Med.* 15: 418-421.

10. Summers B. A., Cummings J. F., deLahunta A. 1995. pp.351-401. Tumors of the central nervous system, *In*: Veterinary Neuropathology (Summers B. A., Cummings J. F., deLahunta A eds), Mosby, St Louis USA.

Figures

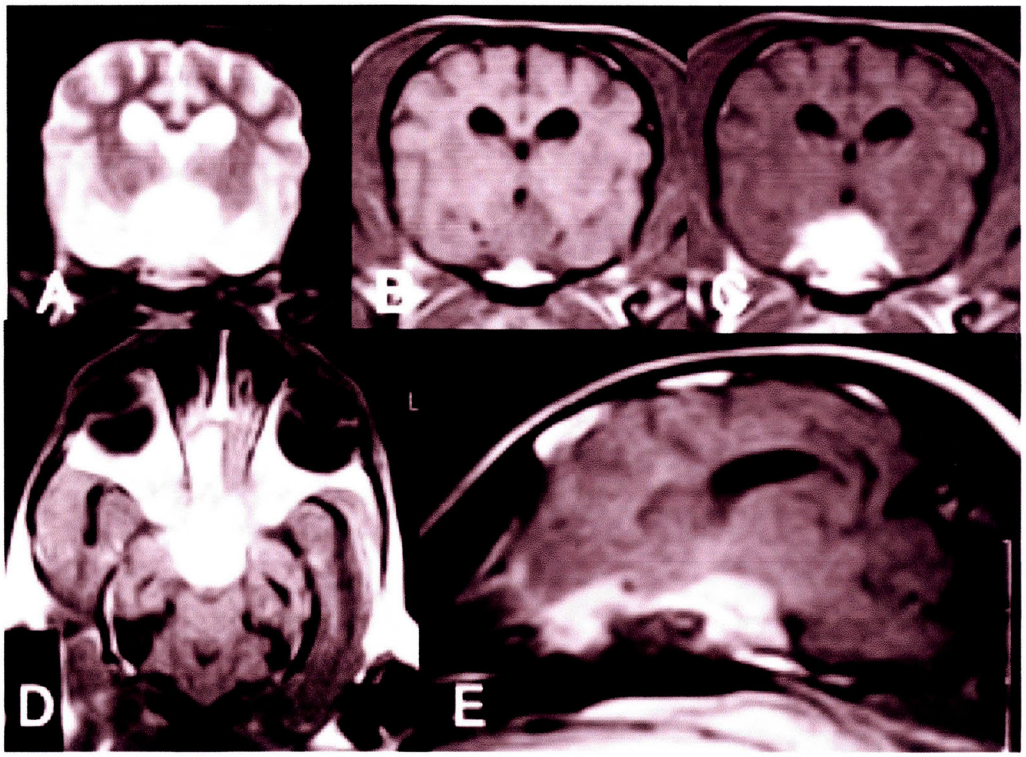

Fig. 1. Brain MRI scans obtained at presentation. A: Transverse T2WI at the pituitary level. B: T1WI at the same level. C: Postcontrast T1WI at the same level. D: Dorsal postcontrast T1WI. E: Sagittal postcontrast T1WI. A tumor mass with marked enhancement can be seen in the extraparenchymal area from the sella turcica to the right olfactory bulb. Edema in the adjacent thalamus can be seen on T2WI. Mass effect can be seen in the sagittal image.

Figures

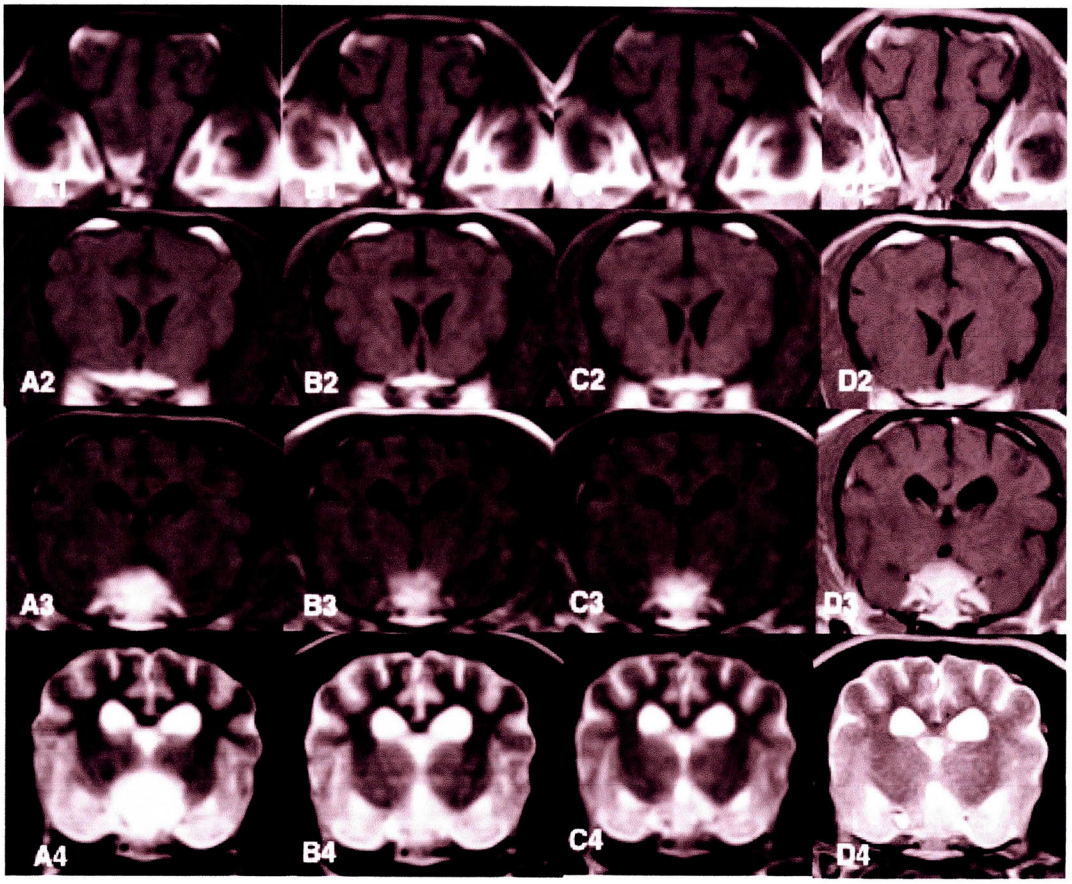

Fig. 2. Changes over the course of treatment as shown by transverse postcontrast T1WIs (1: olfactory level; 2: rostral commissure level; 3: pituitary level) and T2WIs at the pituitary level (4). A: At presentation. B: At 37 days. C: At 5 months. D: At 7 months. At 37 days after presentation, the mass had obviously become smaller, and at 7 months, that re-increased and the size was almost the same as at presentation

Figures

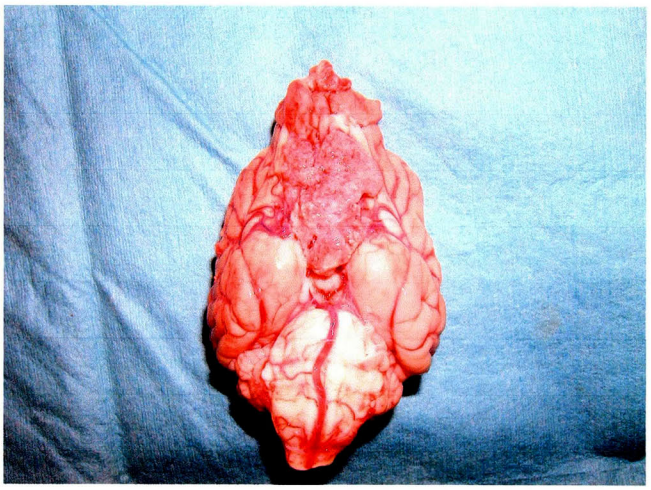

Fig. 3. A: Gross findings at autopsy. The tumor had spread extensively in the skull base.

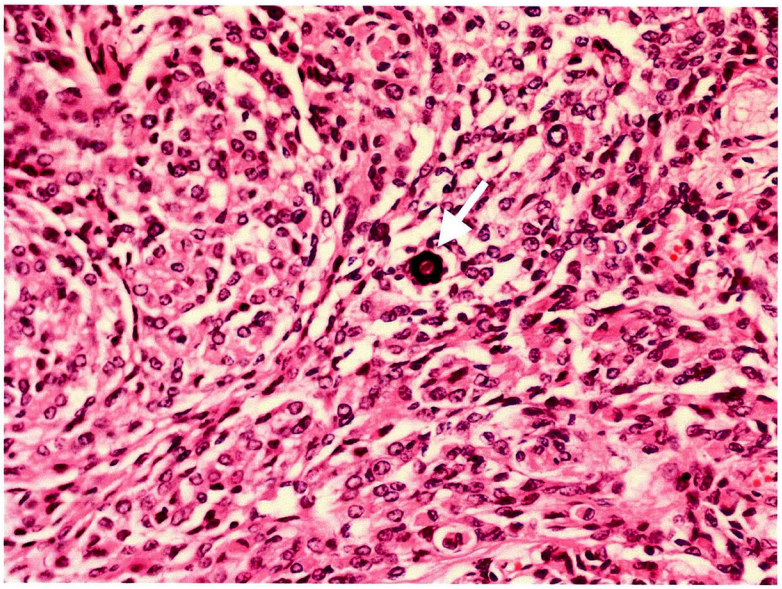

Fig. 3. B: Histopathological features of the neoplastic mass. Solid proliferation of small ovoid to spindle-shaped cells mimicking meningothelial cells with occasional psammoma body formation (arrow). H&E. original magnification x 400.

General Discussion

MRI is considered the most useful diagnostic imaging method in human medicine, and its utility for small animals is being gradually acknowledged in clinical veterinary practice. Here I evaluate the usefulness of MRI for diagnostic imaging cerebral diseases in dogs. In this section, I will summarize each chapter and comprehensively discuss the MRI diagnosis of cerebral diseases in dogs.

In Chapter 1, I describe the case of a dog with intracranial hematoma, and discuss the changes in MR images over time. In this case of spontaneous intracranial hematoma, similar changes were observed in MR images over time as those that are seen in human hematomas and secondary lesions in the surrounding brain parenchyma. This finding will provide a robust basis for future differential diagnosis of intracranial mass lesions in dogs. If rapid antemortem diagnosis becomes possible, more appropriate treatment can be implemented. For example, lesions could be surgically removed, or, as in the case described in Chapter 1, if the symptoms are relatively mild and the hemorrhage does not persist (as seen in longitudinal observations), supportive treatment could be used.

In Chapter 2, I describe two clinical cases of multiple intracranial metastases of thyroid carcinoma in dogs. MRI revealed multiple tumors in the intracranial area, including the pituitary gland. I expect that intracranial or pituitary gland metastases of tumors will be encountered in clinical practice more often in the future, so their differential diagnosis will hopefully be elucidated at a later date. In addition, it is

possible that there exist a large number of nonhormone-producing tumors of the pituitary gland that have been difficult to detect.

In Chapter 3, a case of neuroaxonal dystrophy in a papillon puppy is described in detail. This case had almost the same clinical symptoms and histopathological findings as cases reported by Franklin et al. in 1995. In addition to clinical symptoms and histopathological findings, I also discuss the changes in MRI findings over time, which showed progressive atrophy of the cerebrum, cerebellum and brain stem. These findings confirmed the progressive and degenerative nature of this disease and provide useful information for future antemortem diagnosis when considered in association with information such as the breed of the dog, age (in months) at onset, and clinical symptoms. A number of similar degenerative diseases of the CNS are known in dogs and, therefore, a task for the future is to establish an approach for differential diagnosis using MRI.

In Chapter 4, I describe a canine case of meningioma in the cranial base, which was treated using hydroxyurea chemotherapy. The change in tumor size over time was monitored using MRI, and the reduction in tumor size observed showed that the chemotherapy regimen was effective. Monitoring intracranial tumors using MRI is useful for confirming therapeutic efficacy and modifying the course of treatment, because it can be used to objectively visualize the therapeutic response. In the future, I plan to use MRI to monitor the process of treating brain tumors, encephalitis and other diseases.

For cerebral diseases, the diagnostic procedure starts with estimating the age

of onset, and identifying the pattern of symptoms and other characteristics of the case based on their signalment and information obtained from the owner. Next, neurological and other symptoms at the time of presentation to the practitioner are identified via physical and neurological examinations. When neurological disease is suspected, at this point the location of the lesion(s) is speculated on based on the results of the neurological examination. If the lesion(s) is thought to be located in the CNS, after systemic diseases that influence the nervous system are ruled out via biochemical examinations of blood and urine, specific examinations including MRI, CSF tests, electrophysiological tests and biopsies are performed. By comprehensively considering all the findings from these examinations, a list of differential diagnoses is produced and a course of treatment is determined.

In the cases described in Chapters 1, 2 and 4, MRI examination revealed intracranial mass lesions. Intracranial mass lesions can be tumors, inflamed tissue, abscesses, hemorrhages or a combination of these. In the cases described in Chapter 3, progressive atrophy was observed in the CNS and, therefore, degenerative disease was suspected. Relative to the MRI characteristics of the lesions in other cases, the mass lesion in the case described in Chapter 1 was characterized by having high signal intensity in T1-weighted images from acute to chronic stage, and undergoing changes in signal intensity over time. These characteristics are also observed in intracranial hematoma in humans. In the cases described in Chapter 2, an extraparenchymal mass located in the pituitary gland and a spherical mass on the border between the gray and white matter were observed. The locations of the cerebral masses and their multiplicity

suggested metastatic tumor, but a combination of cerebral intraparenchymal tumor and primary pituitary tumor could not be ruled out. In the case described in Chapter 4, a widespread extraparenchymal mass was observed in the cranial base, which was isointense relative to the surrounding brain parenchyma in T1- and T2-weighted images, had uniform strong enhancement, and showed the dural tail sign. On the basis of these MRI findings, the extraparenchymal large mass lesion in the brain was strongly suspected to be meningioma. However, other diseases, including malignant histiocytosis and lymphoma, are known to produce similar lesions, although their incidences are much lower than that of meningioma. For this reason, a definitive diagnosis of meningioma was not made before the results of the histological examination were obtained. Thus, when carrying out an MR examination of an intracranial mass lesion, several characteristic features were noted, including the location, morphology, and signal intensity of the mass, and the presence or absence of and degree of enhancement. Although the MRI findings did not necessarily permit a definitive diagnosis, they are likely to play an important role in the differential diagnosis of mass lesions. As for conditions other than mass lesions, in the case described in Chapter 3, progressive atrophy was found and degenerative disease was suspected. However, at this point too few cases of this disease this disease have been described to permit identification of the disease-specific patterns of atrophy or changes in signal intensity in MR images; therefore, detection of such patterns is a task for the future.

As mentioned above, a diagnosis (of intracranial hematoma) could be made solely on the basis of MRI findings for the case described in Chapter 1, but MRI

findings alone did not permit a conclusive diagnosis for the cases described in Chapters 2, 3 and 4. In the cases described in Chapter 2, metastatic tumor was thought to be possible because a mass in the thyroid gland area was detected during a physical examination of the whole body, and because a blood test did not indicate Cushing syndrome. In the case described in Chapter 3, neuroaxonal dystrophy was suspected based on signalment and clinical symptoms, and MRI confirmed the presence of an abnormality that was consistent with the clinical features of this disease.

As we have seen, MRI enables CNS lesions to be localized and the type of lesion, for example, mass lesions as seen in the cases described in Chapters 1, 2 and 4, atrophic lesions as seen in the case described in Chapter 3, as well as diffuse inflammatory lesions, to be more accurately determined. In addition, by combining MRI data with signalment, information from the owner, and the results of other examinations in accordance with the procedure for diagnosing neurological diseases that was outlined earlier, diagnosis can be further narrowed down. Thus, MRI data is likely to play an extremely important role in the process of diagnosing these CNS diseases and deciding on a course of treatment. In particular, visualizing lesions using MRI makes it possible to progress to specific treatment such as surgical treatment or radiation therapy as needed.

Over the past few years, while I have been conducting the research presented here, workers both in Japan and abroad have been gathering MRI data from dogs with CNS diseases, and the amount of data available is increasing. MRI is being widely adopted by veterinary care facilities in Japan at a rate that was unthinkable in 2001,

when it was first introduced in my clinic. Case reports including MRI findings are now not infrequently presented at academic meetings. As is the case in medical practice, in small animals practitioners started to use MRI not only for diagnostic purposes at first presentation, but also for monitoring the results of treatment for some diseases, including brain tumors and encephalitis. One example of such use was outlined in Chapter 4, highlighting the utility of using MRI in this way. However, the potential of MRI is far from being fully harnessed in veterinary practice. Interpreting each image thoroughly and obtaining data from more cases would permit image-based diagnoses to become more detailed and accurate in the future. Furthermore, the imaging sequences used in this research were only spin echo T1-weighted images, fast spin echo T2-weighted images and T1-weighted images using contrast medium, but proton density-weighted, gradient echo T2*-weighted and fluid attenuated inversion recovery images are also often used for imaging small animals. There are a variety of other methods using different imaging sequences, including a method that distinguishes fat and water, diffusion-weighted images and MR angiography, but there is virtually no report on the application of these methods in animals. More detailed differential diagnosis will become possible in the future when these and other newly developed sequences are used.

Diagnostic imaging for CNS diseases advanced considerably with the introduction of MRI. Relative to humans, in small animals markedly fewer CNS diseases have been named, and there is a larger number of idiopathic diseases, indicating that these diseases have been insufficiently classified according to their

causes. Therefore, establishing a more detailed classification of these diseases and their diagnostic methods would be clinically important. To achieve this, it is crucial to continue keeping detailed treatment records for each clinical case, as these records represent valuable data. In addition, it is necessary to further improve the accuracy of diagnosis of CNS diseases by considering other diagnostic methods, such as electrophysiological tests, molecular biological tests and tests for potential disease-specific markers in the CSF, including anti-astrocyte autoantibody, which has been tested for in very few cases reported in the literature. Further improvements will be achieved also by accumulating reports in which the findings of various examinations including MRI and the results of histopathological diagnosis are comprehensively analyzed. Furthermore, there are diseases in dogs (e.g. Borna disease) for which only a tiny number of cases have been reported so far, and the number of such diseases can be expected to increase. The epidemiological and pathological features of these newly encountered diseases should also be studied in the future. Additionally, I speculate that because two Japanese people died from rabies in November 2006, measures against rabies, including education campaigns encouraging people to be immunized against rabies, and inclusion of rabies in the differential diagnosis for dogs with CNS symptoms, will be considered more important than before.

The number of diseases that can be diagnosed before an animal's death needs to be increased by collecting information regarding diagnosis via the actions I described above relating to the observation of clinical cases. At the same time, attention should be directed also to elucidating the pathology of CNS diseases in cats and dogs, and

focusing surgical and medical treatment on the causes of these diseases. I consider that these are relatively unexplored themes.

So far, I have discussed the MRI diagnosis of CNS diseases in dogs from the academic perspective of veterinary medicine. From a slightly different standpoint, that of a small animal practitioner, I believe that specialized examination, diagnosis and treatment of animals at secondary care facilities after referral by general practitioners' facilities should benefit not only the animals and their owners but also the general practitioners who refer these cases. General practitioners would benefit in two ways. First, a benefit that general practitioners are already receiving is the feeling of security of being unburdened of a difficult case, knowing that the animal and its owner will return once the disease resolves. Second is another benefit that I think general practitioners should receive, which is academic feedback with respect to the outcomes of treatment and new information generated by the referred cases. Secondary care facilities should directly and indirectly feed back the information collected from the accrued clinical cases that they have treated, for example regarding what type of disorder should be suspected on the basis of which symptoms, or in what situations cases need to be urgently referred to secondary care facilities, so that the cases can be referred as smoothly as possible.

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Lastly, I dedicate this thesis to the five dogs, Sara, Mari, Takkun, Eve and Chris, who provided valuable data that will help dogs suffering from similar diseases in the future; I pray for the souls of these dogs.