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Case Report
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Pituitary Macrotumor Causing Narcolepsy-Cataplexy in a Dachshund

S. Schmid, A. Hodshon, S. Olin, I. Pfeiffer, and S. Hecht

Familial narcolepsy secondary to breed-specific mutations in the hypocretin receptor 2 gene and sporadic narcolepsy associated with hypocretin ligand deficiencies occur in dogs. In this report, a pituitary mass is described as a unique cause of narcolepsy-cataplexy in a dog. A 6-year-old male neutered Dachshund had presented for acute onset of feeding-induced cataplexy and was found to have a pituitary macrotumor on magnetic resonance imaging (MRI). Cerebral spinal fluid hypocretin-1 levels were normal, indicating that tumor effect on the ventral lateral nucleus of the hypothalamus was not the cause of the dog's narcolepsy-cataplexy. The dog was also negative for the hypocretin receptor 2 gene mutation associated with narcolepsy in Dachshunds, ruling out familial narcolepsy. The Dachshund underwent stereotactic radiotherapy (SRT), which resulted in reduction in the mass and coincident resolution of the cataplectic attacks. Nine months after SRT, the dog developed clinical hyperadrenocorticism, which was successfully managed with trilostane. These findings suggest that disruptions in downstream signaling of hypocretin secondary to an intracranial mass effect might result in narcolepsy-cataplexy in dogs and that brain MRI should be strongly considered in sporadic cases of narcolepsy-cataplexy.

Key words: hypocretin; hypothalamus; stereotactic radiotherapy.

A 6-year-old male neutered Dachshund was referred to the University of Tennessee Veterinary Medical Center's Internal Medicine Service for an acute onset of collapsing while eating of 20 days' duration. The owners reported that the collapse episodes occurred 30–40 seconds after the initiation of feeding, which was twice daily. Since the onset of signs, every meal was associated with a single collapse episode except one meal, which was associated with two episodes. The collapse episodes only occurred while eating and were characterized by a sudden fall to the floor with a quick recovery and return to eating (see supplemental video). The dog was also described to be more lethargic and have drooped eyelids since the onset of episodes.

Two weeks before admission, the referring veterinarian performed a CBC and serum biochemical profile, which were both within normal limits. Thoracic radiographs showed collapsed intervertebral disk spaces at T11-12 and T12-13 but were otherwise normal. The dog was treated for suspected intervertebral disk disease (IVDD) with meloxicam[a] and methocarbamol[b] and failed to improve. Hand-feeding one kibble at a time with vigorous petting prevented collapse episodes although the dog still staggered and became drowsy during feeding.

Abbreviations:

CNS	central nervous system
CSF	cerebrospinal fluid
DWI	diffusion-weighted imaging
FLAIR	fluid-attenuated inversion recovery
GRE	gradient recalled echo
IVDD	intervertebral disk disease
MRI	magnetic resonance imaging
SE	spin echo
SRT	stereotactic radiotherapy

On presentation, the dog was moderately overweight (BCS 7/9) but otherwise had a normal physical examination. The neurologic evaluation was normal other than moderate pain elicited on palpation of the caudal cervical and mid-lumbar spine, consistent with suspected concurrent IVDD. Abnormalities were not detected on thoracic radiographs, abdominal radiographs, or abdominal ultrasound. Feeding a meal in the hospital elicited a cataplectic event characterized by buckling of the hind limbs and drooping of the neck, followed quickly by complete collapse to the floor. The dog recovered within 1.5 seconds and returned to eating. During this event, there was no change in the ECG tracing, eliminating the possibility of an underlying cardiac disorder resulting in syncope. The observation of cataplexy, which is pathognomonic for narcolepsy, provided a diagnosis of narcolepsy in this dog. The dog was tested for the hypocretin receptor 2 gene mutation[c] identified in a family of narcoleptic Dachshunds[1] and was negative for the mutation.

Given the unusual finding of acute onset cataplexy in an older Dachshund, brain magnetic resonance imaging (MRI) was performed under general anesthesia with a 1.5T magnetic resonance system.[d] The pulse sequences

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obtained included sagittal and dorsal T2-W spin echo (SE); transverse T2-W SE, T1-W SE, PD-W SE, T2-W fluid-attenuated inversion recovery (FLAIR), T2*-W gradient recalled echo (GRE), and diffusion-weighted imaging (DWI); transverse T1-W GRE with fat saturation, and transverse, sagittal, and dorsal with fat saturation T1-W SE after contrast medium administration. A $1.8 \times 1.6 \times 1.8$ cm smoothly marginated, expansile mass originating from the middle fossa was found extending dorsally to the ventral aspect of the interthalamic adhesion and caudally to the midbrain. The mass was heterogeneously T2 and FLAIR hyperintense, T1 isointense, and did not show susceptibility artifact on T2*-W imaging. After intravenous contrast[e] administration, the mass strongly and slightly heterogeneously enhanced. The mass occupied over 40% of the dorsoventral height of the cranial vault (Fig 1). The imaging findings were most consistent with a pituitary macroadenoma; however, an invasive adenoma or carcinoma was also considered. Other etiologies of suprasellar masses (neoplastic such as suprasellar germ cell tumors or non-neoplastic such as granulomatous disease) were considered less likely but could not be entirely excluded. The mass was suspected to be nonfunctional at the time of diagnosis on the basis of a lack of physical examination and clinicopathologic findings suggestive of hyperadrenocorticism.

Cerebrospinal fluid (CSF) was collected from the cerebellomedullary cistern after intravenous administration of mannitol (0.5 g/kg). Routine analysis was not performed because of the limited quantity obtained. The CSF was frozen at −80°C until being shipped overnight to the Center for Narcolepsy at the Stanford School of Medicine. Hypocretin-1 levels[f] were determined to be normal (328.7 (ref. 200–350) pg/mL). The dog recovered uneventfully and was discharged from the hospital on gabapentin[g] (7 mg/kg PO q 8h), prednisone[h] (0.6 mg/kg PO q24h), and the serotonin reuptake inhibitor venlafaxine[i] (6 mg/kg PO q24h). Venlafaxine was prescribed to treat the observed cataplexy but was discontinued after two doses because of excessive sedation and lack of perceived response.

Transsphenoidal hypophysectomy was not recommended because of the large dimensions of the mass. Instead, the dog underwent stereotactic radiotherapy (SRT) delivered via an intensity-modulated radiation therapy technique four weeks after diagnosis. A total dose of 24 Gy was delivered in three consecutive daily fractions of 8 Gy each with a Clinac iX[j] linear accelerator. Port films were taken on the first day of treatment to confirm and if needed adjust the dog's positioning before treatment. Port films were repeated each day of treatment to confirm and adjust the dog's positioning as needed. An anti-inflammatory dosage of prednisone

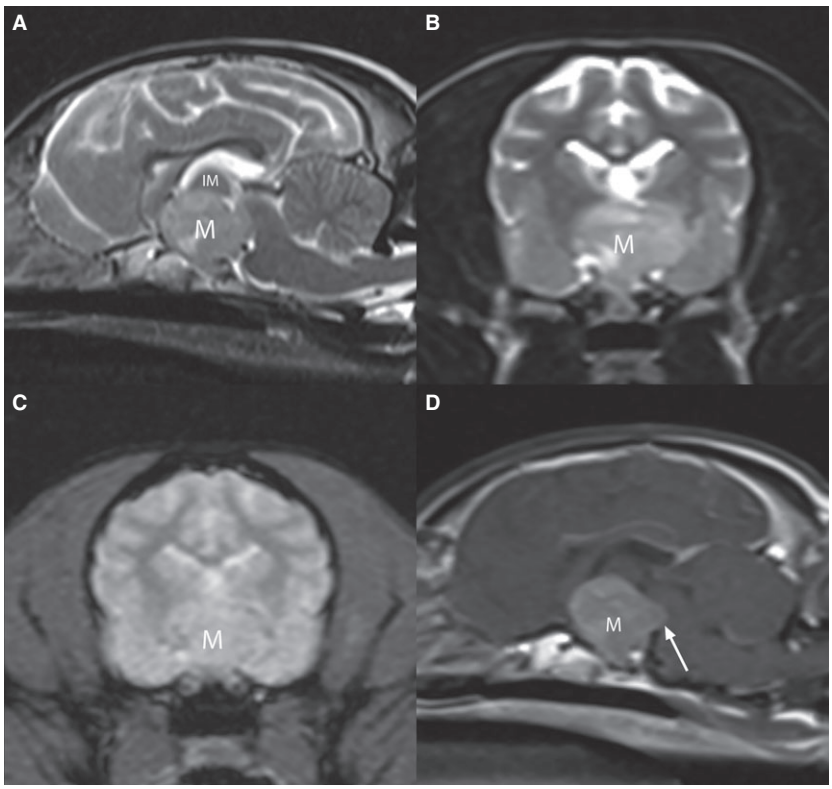

Fig 1. Magnetic resonance images in a 6-year-old Dachshund with narcolepsy-cataplexy. Sagittal T2-W **(A)**, transverse T2-W **(B)**, transverse T2*-W **(C)** images, and sagittal T1-W **(D)** image after contrast medium adminstration show a large suprasellar mass (M). The mass compresses the interthalamic adhesion (IM) from ventrally, with complete obliteration of the 3rd ventricle between the interthalamic adhesion and the mass **(A).** The mass is heterogeneously T2 hyperintense **(A, B)** and does not show evidence of intralesional hemorrhage **(C).** The mass is strongly contrast enhancing and focally bulges caudally **(D**; arrow).

(0.6 mg/kg PO q24h) was continued during radiation therapy. Starting three weeks after SRT, the prednisone dosage was tapered by 25% every two weeks and was discontinued four months after radiation therapy.

After radiation therapy, the owners continued feeding the dog one kibble at a time with vigorous petting, and he did not have any cataplectic events until four weeks after SRT when one event occurred in response to being offered two pieces of steak. Six weeks after SRT, the owners began feeding the dog normally (no longer one kibble at a time with petting), and he was noted to sink in the hind end while eating but did not fully collapse. Eight weeks after SRT, the dog began to eat much more quickly and had no evidence of cataplexy while eating. His lethargy persisted, with only mild increases noted in his activity level after SRT.

A neurologic examination was repeated six months after SRT, and the only abnormal finding was mild pain on palpation of the mid-lumbar spine. The dog seemed subjectively brighter and more interactive than he had on initial examination. Despite the owners noting an increase in appetite, the dog had lost 0.6 kg since his initial presentation. A repeat MRI was performed by the same protocol listed above. The suprasellar mass was mildly decreased in size (1.7 × 1.5 × 1.4 cm) and more heterogeneous with intralesional susceptibility artifacts on T2*-W images consistent with hemorrhage. There was decreased mass effect compared to the original MRI, resulting in less compression of the midbrain and third ventricle (Fig 2). Three days after repeat MRI (25 weeks after SRT), the dog had a single isolated cataplectic event while feeding.

Thirty-seven weeks after SRT, the dog acutely developed panting, polyuria, and polydipsia. He also had another brief cataplectic event associated with feeding. The dog was represented for evaluation and had a mild increase in his plasma alkaline phosphatase (302 [ref. 13–240] U/L) and alanine transaminase (116 [ref. 18–100] U/L) activities. A repeat abdominal ultrasound revealed bilateral adrenomegaly (right 0.78 cm, left 0.72 cm) compared to that at presentation (right 0.58 cm, left 0.47 cm). An ACTH stimulation test confirmed the suspicion of hyperadrenocorticism (baseline cortisol 3.6 mcg/dL, 1 hour after cosyntropin cortisol 29.4 mcg/dL). The dog's panting, polyuria, and polydipsia improved after the initiation of trilostane[k] (2 mg/kg PO q12h) treatment. At the time of this report (9 months after SRT), the dog has had a total of three cataplectic events (4, 25, and 37 weeks after SRT) since SRT.

Narcolepsy is a chronic sleep disorder characterized in humans by hypersomnia (excessive daytime sleepiness), cataplexy (a sudden and inappropriate loss of muscle tone in response to emotional stimulation), sleep paralysis, and hypnagogic hallucinations; only the

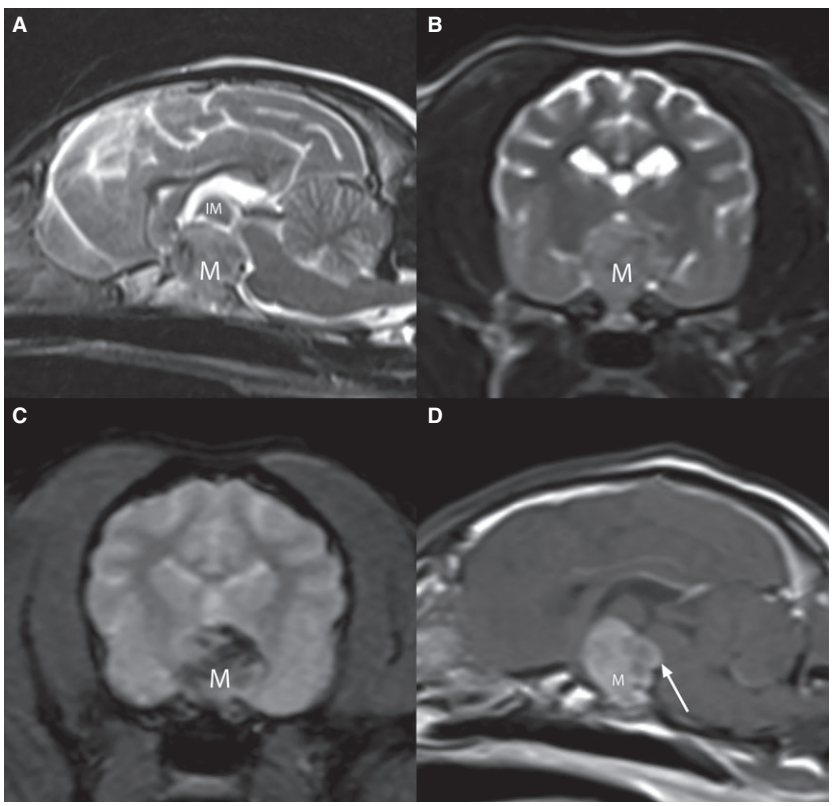

Fig 2. Repeat MR examination in the same dog after SRT. Sagittal T2-W **(A),** transverse T2-W **(B),** transverse T2*-W **(C)** images, and sagittal T1-W **(D)** image after contrast medium administration show an overall decrease in size and increased heterogeneity of the mass (M) with extensive hypointense susceptibility artifacts indicative of intralesional hemorrhage **(C)**. There is decreased mass effect indicated by visibility of the hyperintense 3rd ventricle between the mass (M) and the interthalamic adhesion (IM) **(A)**. The caudal protrusion of the mass is also decreased in size **(D).**

first two manifestations have been documented in veterinary patients.[2–4] Narcolepsy can be primary or secondary, and two forms of primary narcolepsy are described.[2] Type 1 primary narcolepsy is caused by selective loss of hypothalamic neurons that produce the neuropeptide hypocretin (also called orexin), resulting in low levels of hypocretin in the CSF.[5] These neurons are located in the ventral lateral hypothalamic nucleus in dogs and have extensive connections throughout the central nervous system (CNS) that promote wakefulness and muscle tone in response to the release of hypocretin.[6] Humans with primary narcolepsy who suffer from cataplexy as part of their disease are classified as type 1, and the majority have low or undetectable levels of hypocretin in the CSF.[7–9] In type 2 primary narcolepsy, cataplexy is not a component, and CSF hypocretin levels are normal. The cause of type 2 primary narcolepsy is not known.[5] The underlying etiology of both types of primary narcolepsy is thought to be multifactorial, with genetics playing a role in each.[10]

Secondary narcolepsy, more correctly called symptomatic narcolepsy, has rarely been reported in humans and can result from brain tumors, stroke, demyelination, traumatic injury, and encephalitis.[11–16] Between 1969 and 2005, 116 human cases of symptomatic narcolepsy-cataplexy were reported. Thirty-three (29%) of these cases were associated with a brain tumor, with the majority of lesions (70%) being found in the hypothalamus or adjacent structures (pituitary, suprasellar, or optic chiasm).[17]

Both familial and sporadic forms of narcolepsy have been described in dogs.[18] Familial narcolepsy in dogs has an autosomal recessive transmission pattern in Dobermans, Labrador retrievers, and Dachshunds, with clinical signs usually evident by 6 months of age.[18,19] Familial narcolepsy is caused by breed-specific mutations in the hypocretin receptor 2 gene. This gene encodes the receptor for hypocretin found predominantly in the locus ceruleus and dorsal raphe nuclei, which in dogs are located in the pons and mesopontine junction, respectively.[20] CSF hypocretin concentrations are normal in these dogs, and the abnormal receptor prevents ligand binding and activation of downstream pathways.[1,21] Sporadic forms of canine narcolepsy are less common and can occur in dogs of any age. The mean age of onset of sporadic narcolepsy in one study was 2.4 years.[18] These cases are primarily associated with reduced CSF hypocretin concentrations, the cause of which is unknown. However, rare cases of sporadic narcolepsy occur without documented central hypocretin deficiencies. A cat found collapsed beside a road reportedly exhibited transient cataplexy for approximately 10 days, suggesting that minor brain stem trauma might lead to cataplexy.[22] In addition, transient feeding-induced cataplexy lasting approximately one week has been observed in a few Dachshunds after surgical correction of herniated thoracolumbar intervertebral disks. These dogs were suspected to have a mutation in the hypocretin receptor 2 gene that resulted in clinical signs only when their CNS was exposed to a general anesthetic.[22]

This report describes a dog with symptomatic narcolepsy-cataplexy secondary to a middle fossa tumor. An electroencephalogram was not performed to rule out the possibility of unusual seizure activity causing the collapse episodes; however, the clinical sign of cataplexy is pathognomonic for narcolepsy in humans and was therefore considered sufficient to make the diagnosis in this case.[23] The dog presented here was negative for the hypocretin receptor 2 gene mutation associated with narcolepsy in Dachshunds, ruling out familial narcolepsy. In addition, he had normal CSF hypocretin concentrations, suggesting that a tumor effect on the ventral lateral nucleus of the hypothalamus was not the cause of his narcolepsy-cataplexy. Rather, the function of one or more nuclei downstream in the pathway, such as the pontine and mesopontine nuclei involved in wakefulness, might have been compromised by the caudal protrusion of this tumor in such a way as to cause the specific clinical sign of cataplexy. This speculation is supported by the regression of this protrusion after SRT coincident with resolution of the dog's cataplectic attacks. The dog's continued lethargy could be caused by persistent mass effect compressing the reticular activating system, ongoing hypersomnolence as a residual manifestation of narcolepsy, or both. The resolution of the dog's cervical pain suggests that it may have been referred pain from the tumor that also responded to SRT.[24] However, this is only speculation, as it could also have been caused by a mild intervertebral disk herniation (or another undiagnosed condition) that resolved over time.

The Dachshund's overweight body condition on presentation might have also been associated with interruption of pathways originating in the hypothalamus that are important for energy balance. Hypocretin peptides were originally described as modulators of food intake, with central administration of hypocretin enhancing food intake in rodents.[25] Despite this observation, body mass indices have been found to be increased rather than decreased in narcoleptic humans, with the most marked increases in body mass indices seen in those with undetectable CSF hypocretin levels.[25,26] Also, hypocretin deficiency might not be as important as deficiencies of other neuropeptides that are colocalized in neurons that produce hypocretin. This is supported by the fact that hypocretin knockout mice have a normal body weight, whereas genetic ablation of hypocretin neurons in mice has been shown to result in weight gain despite an almost 30% reduction in food intake.[27] After SRT, the dog presented here exhibited weight loss and an increased appetite. This could have been because of prednisone administration, although the effect persisted after prednisone was discontinued. Alternatively, it is possible that decreased mass effect after SRT resulted in return of normal signaling important in energy balance. Improved wakefulness in this dog with treatment of his narcolepsy could have also contributed to increased physical activity and energy expenditure.

In conclusion, this case documents that narcolepsy with cataplexy can result from space-occupying masses in the canine brain, much like that described in humans with symptomatic narcolepsy. A brain MRI should be strongly considered in sporadic cases of narcolepsy-cataplexy to rule out intracranial causes, particularly in

dogs in which familial narcolepsy is considered unlikely because of either their signalment or neurologic examination findings. In addition to previously described hypocretin receptor mutations and hypocretin ligand deficiencies, this case report suggests that disruptions in the downstream signaling of hypocretin might result in narcolepsy-cataplexy in dogs.

Footnotes

[a] Metacam, Boehringer Ingelheim Vetmedica, Inc., Ridgefield, CT
[b] Robaxin, West-Ward Pharmaceuticals Corp., Eatontown, NJ
[c] Paw Print Genetics™, Genetic Veterinary Sciences, Inc., Spokane, WA
[d] Magnetom Espree™, Siemens Medical Solutions, Malvern, PA
[e] Magnevist (469.01 mg/mL gadopentetate dimeglumine), Bayer Heath Care LCC, Whippany, NJ
[f] Center for Narcolepsy, Stanford University of Medicine, Stanford, CA
[g] Neurontin, Pfizer Inc., New York, NY
[h] Prednisone, West-Ward Pharmaceuticals Corp., Eatontown, NJ
[i] Effexor, XR, Pfizer Inc., New York, NY
[j] Clinac iX Linear Accelerator, Varian Medical Systems Inc, Palo Alto, CA
[k] Vetoryl, Dechra Veterinary Products Limited, Hadnall, Shrewsbury, UK

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Conflict of Interest Declaration:Authors declare no conflict of interest.

Off-label Antimicrobial Declaration:Authors declare no off-label use of antimicrobials.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Video S1. Cataplexy in a 6-year-old Dachshund with Narcolepsy. Thirty seconds into a meal, the dog demonstrates a sudden collapse to the floor with a quick recovery and return to eating.