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**What Is Your Neurologic Diagnosis?**

This report was submitted by Theophanes Liatis, DVM; Konstantina Theodorou, DVM, PhD; Dimitris Kasabalis, DVM; Nectarios Soubasis, DVM, PhD; Ioannis Panopoulos, DVM, PhD; and Zoe Polizopoulou, DVM, PhD; from the Neurology and Neurosurgery Service, Small Animal Hospital, School of Veterinary Medicine, University of Glasgow, Glasgow, G61 1BD, Scotland (Liatis); Companion Animal Clinic (Theodorou, Soubasis) and Diagnostic Laboratory (Polizopoulou), School of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki, 546 27, Greece; Attica Animal Hospital, Peania, 190 02, Greece (Theodorou); Agios Modestos Veterinary Clinic, Oreokastro, 570 13, Greece (Kasabalis); and Alphavet Veterinary Diagnostic Imaging Center, Nea Kifissia, 145 64, Greece (Panopoulos).

Address correspondence to Dr. Liatis (theofanis.liatis@gmail.com).

A 6-year-old, 12 kg (26.5 lb), stray, intact male crossbreed dog that had been rescued 6 months earlier developed episodes of weakness and collapse of pelvic or all limbs during walking or exercise. The owners also had noticed a general decrease of food intake in the light of a normal appetite and excessive daytime sleepiness. On admission, clinical examination findings were unremarkable.

**Neurologic Examination:**

**Observation**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mental | Alert | X | Depressed |  | Disoriented |  | Stupor |  | Coma |  |
| Posture | Normal | X | Head tilt |  | Tremor |  | Falling |  |  |  |
| Gait | Normal | X | Ataxia |  | Pelvic limbs |  | All 4 |  | Circling |  |
| Paresis | Pelvic limb |  | Tetra |  | Hemi |  | Mono |  |  |  |
| Other | An episode of partial (pelvic limbs) collapse during walking or exercise was noticed during gait assessment **(Figure 1)**. This collapse included sudden discontinuation of walking and reluctance to continue for some seconds after sudden pelvic limb collapse (paresis). Consciousness was present, and the dog was quickly returning back to normal activity **(Supplementary Video 1)**. |

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|  | Key: 4 = exaggerated, clonus; 3 = exaggerated; 2 = normal; 1 = diminished; 0 = none; NE = not evaluated |
|  |  |  |  |  |  |  |  |  |
| **Postural reactions** | Left forelimb | Right forelimb | Left hind limb | Right hind limb |
| Wheelbarrow | 2 | 2 |  |  |
| Hopping | 2 | 2 | 2 | 2 |
| Ext postural thrust |  |  | 2 | 2 |
| Proprioceptive pos | 2 | 2 | 2 | 2 |
| Hemistand/walk | 2 | 2 | 2 | 2 |
| Placing-tactile | NE | NE |  |  |
| Placing-visual | 2 | 2 |  |  |
| **Spinal reflexes** |  |  |
|  | Left forelimb | Right forelimb | Left hind limb | Right hind limb |
| Quadriceps |  |  | 2 | 2 |
| Extensor carpi | 2 | 2 |  |  |
| Flexion | 2 | 2 | 2 | 2 |
| Crossed extensor | 2 | 2 | 2 | 2 |
| Perineal  |  |  | 2 | 2 |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cranial nerves** |  |  |  |  |  |  |  |
|  | **L** | **R** |  | **L** | **R** |  | **Comments** |
| II, VII-Vision menace | 2 | 2 | VIII-Nystagmus, resting | 2 | 2 |  |  |
| II, III-Pupils resting | 2 | 2 | VIII-Nystagmus, change | 2 | 2 |  |
| Stim L | 2 | 2 | V-Sensation | 2 | 2 |  |
| Stim R | 2 | 2 | VII-Facial mm | 2 | 2 |  |
| II-Fundus | NE | NE | V, VII-Palpebral flex | 2 | 2 |  |
| III, IV, VI-Strabismus, resting | 2 | 2 | IX, X-Gag | 2 | 2 |  |
| III, IV, VI, VIII-Strabismus, position | 2 | 2 | XII-Tongue | 2 | 2 |  |

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| --- | --- |
| **Sensation** (Locate and describe abnormal) |  |
| Hyperesthesia | 2 | No evidence of hyperesthesia. |
| Superficial pain | NE | Not evaluated because of normal ambulation. |
| Cutaneous reflex | 2 |  |
| Deep pain | NE | Not evaluated because of normal ambulation. |

**What is the problem? Where is the lesion? What are the most probable causes of this problem? What is your plan to establish a diagnosis? Please turn the page**.

**Assessment**

 **Anatomic Diagnosis**

|  |  |
| --- | --- |
| **Problem** | **Rule out location** |
| Episodes of partial collapse (mainly of the pelvic limbs) with intact consciousness and quick recovery, provoked by walking or exercise  | Sleep centers and pathways (reticular formation of brainstem, hypothalamus, forebrain, or spinal cord) if related to cataplexy.Muscle, peripheral nerve, or neuromuscular junction if related to exercise-induced neuromuscular paresis.Myocardium if related to syncope. |

 **Likely location of one lesion**

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| Sleep centers (reticular formation of brainstem or the hypothalamus) were the most likely lesion location for episodes of collapse without proven exercise intolerance or other cardiological signs. |

**Etiologic diagnosis—**Differential diagnoses for a 6-year-old dog with episodes of collapse and normal inter-episode neurologic examination findings included cataplexy (eg. narcolepsy), exercise-induced neuromuscular paresis (eg, myasthenia gravis or polymyositis), syncope (eg, cardiac arrhythmia), or epileptic seizures (eg, idiopathic epilepsy, hypocalcemia, hypoglycemia, hepatic encephalopathy, toxic encephalopathy, congenital encephalopathy, meningoencephalitis, head trauma, or brain neoplasia). The initial diagnostic plan included a CBC, serum biochemical analysis, and urinalysis to evaluate the dog’s general condition and rule out metabolic diseases. Cardiological evaluation, including Doppler ultrasonographic arterial blood pressure measurement, thoracic and abdominal radiography, ECG, echocardiography, and serologic testing for heartworm (*Dirofilaria immitis*),a was performed to assess for possible syncopal episodes. To investigate for myasthenia gravis, serologic testing for anti-acetylcholine receptor antibodies and an edrophonium chloride test were performed. Then, to investigate for sleep disorders and confirm suspected cataplexy, a clinical food-elicited cataplexy test1 was used. Thereafter, an atropine suppression test was conducted. Finally, to identify or exclude primary or secondary (symptomatic) disease, brain MRIb and analysis of a CSF sample were performed, along with measurement of CSF hypocretin-1 concentration for confirmation of narcolepsy.

**Diagnostic test findings—**The CBC revealed mild eosinophilia (1,200 eosinophils/μL; reference interval, 0 to 600 eosinophils /μL), which was indicative of a possible parasitic infestation in light of a lack of previously administered antiparasitic prevention. Serum biochemical and urinalysis findings were unremarkable.

 Cardiological evaluation, both in a neutral phase and during an episode of collapse, revealed a normal vagal arrhythmia with an otherwise unremarkable heart function. Serologic testing for heartworm yielded a negative result. At that time, a Holter monitor was not available for evaluation of heart rhythm during a 24-hour period; however, given the dog’s apparently normal cardiological findings, a possible arrhythmogenic cardiomyopathy was considered unlikely.

An edrophonium chloride test was performed. Following IV administration of 0.1 mg of edrophonium chloride/kg (*0.22 mg/lb* ), the dog did not respond and continued having collapse episodes after feeding or periods of excitement or exercise. Serologic testing for anti-acetylcholine receptor antibodiesc yielded negative results. Acquired myasthenia gravis was considered a less likely diagnosis, although given the unknown history of the dog, congenital myasthenia gravis remained among the differential diagnoses.

A food-elicited cataplexy test1 was performed by providing the dog with 10 small (0.5 cm3) pieces of food that were placed on the floor at 30-cm distance apart (Supplemental video 1). The dog needed encouragement to eat, and an episode of complete collapse was elicited soon after the initial food intake (Figure 1). During the episode, the dog intermittently became flaccid tetraparetic, remaining in sternal recumbency and simultaneously falling asleep for a couple of minutes.

Given the nature of the episodes (cataplexy), narcolepsy was suspected and an atropine suppression test was performed. Atropine (0.1 mg/kg [0.22 mg/lb]) was administered as a single IV bolus. Then, food was offered to the dog as per abovementioned protocol or as a single bowl course, and the dog did not have an episode of collapse after food consumption (Supplementary video 1). On the basis of the response to the atropine suppression test, the dog’s episodes of collapse were considered episodes of cataplexy, and a presumptive diagnosis of narcolepsy was made. Specifically, the episodes after walking or exercise characterized by weakness of pelvic limbs with intact consciousness and quick recovery were considered as partial cataplectic episodes, whereas the postprandial episodes represented by complete collapse and induction of sleep were considered as complete cataplectic episodes.

Owing to the unknown history of the dog, the owners elected to proceed with MRI of the brain and CSF sample analysis to determine whether narcolepsy was primary or secondary. A specialist certified by the European College of Veterinary Diagnostic Imaging evaluated the MRI images of the brain, which included T1-weighted spin-echo, T2-weighted spin-echo, and T2 FLAIR (before and after IV administration of gadoterate meglumine). The MRI findings were unremarkable. A cerebellomedullary cisternal CSF sample was analyzed, and results were within reference limits (total microprotein concentration, < 30 mg/dL [reference interval, < 30 mg/dL]; total nucleated cell count, 0 cells/μL [reference interval, 0 to 5 cells/μL]). A thoracic and abdominal radiography was performed to investigate for extracranial disease and revealed to be normal. At that point, a CSF sample was sent to a reference laboratory for evaluation of hypocretin-1 concentration,d which was low (82 pg/mL; reference interval,2 250 to 350 pg/mL). Consequently, a definite diagnosis of primary narcolepsy was made for the dog.

Treatment with imipramine hydrochloride, a tricyclic antidepressant, was initiated at a dosage of 2.0 mg/kg (0.9 mg/lb), PO, every 12 hours for 5 days but there was no response. The dosage was modified to 1.0 mg/kg (0.45 mg/lb), PO, every 8 hours for 20 days, and a decrease in the frequency and intensity of cataplectic episodes was noted. A subsequent modification of the imipramine hydrochloride dosage to 2 mg/kg, PO, every 8 hours for 4 days resulted in the dog becoming obtunded. Subsequently, a dosage of 1.5 mg/kg (0.68 mg/lb), PO, every 8 hours was selected, and the dog’s condition improved. With that treatment regimen, the dog had 0 or 1 episode of collapse/d (partial cataplexy) involving only a transient weakness of pelvic limbs either after exercise or feeding. The dog remained in a well-controlled condition for a period of 4 months, at which time it was lost to follow-up.

**Comments**

Narcolepsy is a rapid-eye movement (REM) sleep disorder that results in excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Narcoleptic syndrome represents an abrupt occurrence of REM sleep without a preceding period of slow-wave sleep as a consequence of pathological changes in the REM sleep center (mainly the reticular formation of the brainstem).3 Narcolepsy can be primary or secondary.4 In humans, primary narcolepsy is classified as type 1 narcolepsy (wherein the CSF concentration of hypocretin, a hypothalamic neuropeptide, is low) or type 2 narcolepsy (wherein the concentration of hypocretin is within the reference interval).4 In dogs, it is known that some breeds (eg, Doberman Pinschers, Labrador Retrievers, and Dachshunds) develop primary narcolepsy because of hereditary mutations in the hypocretin receptor 2 gene.3,5 In these dogs, the CSF hypocretin-1 concentration is within the reference interval3; however, measurement of CSF hypocretin-2 concentration is low-to-undetectable that might reflect a difference in secretion, turnover, or stability of hypocretin-2 compared to hypocretin-1.2 Instances of narcolepsy in Dachshunds that underwent induction of anesthesia for thoracolumbar surgery have also been reported.3 The secondary form of narcolepsy can develop in any breed of dog and is a result of loss of production of hypocretin peptides because of a primary disease that affects the neurons of the ventral lateral nucleus of the hypothalamus (eg, distemper encephalitis,6 meningoencephalitis of unknown origin,3,4 or pituitary tumor7).3,5 Low CSF hypocretin-1 concentrations have been identified in those dogs.3,5

The most noticeable clinical sign of narcolepsy in affected animals is cataplexy,3,5 which is a unique sign of narcoleptic syndrome and is characterized by sudden collapse as result of muscle atonia (which is the state of muscles during normal REM sleep) in response to emotional stimulation.3,5 Emotional stimulation may include excitement, provision of food, engagement in play, or sexual arousement.3,5 Cataplexy can be partial or complete. Partial cataplexy involves a short period of flaccid paraparesis or flaccid tetraparesis with retention of consciousness, and is easily interrupted by external stimuli.5 Partial cataplexy can be misinterpreted as exercise-induced neuromuscular paresis.3 In comparison, episodes of complete cataplexy have a longer duration, and manifest as flaccid tetraparesis to falling asleep(often with REM, muscle twitching, or slow repetitive limb movements).5 Cataplexy should not be confused with catalepsy, as the latter refers to a state of pronounced motor inhibition characterized by a failure to correct an externally imposed awkward posture. Catalepsy is a phenomenon of passive defensive behavior among vertebrates (eg, rabbits) in the presence of a predator; in humans, an exaggerated form of catalepsy is the syndrome of schizophrenia.8 Excessive daytime sleepiness is another clinical sign that can be obtained from the history, but such a finding is subjective and can be unreliable because in general dogs frequently sleep for brief intervals during the day.5 Sleep paralysis is not a recognizable sign in animals, but periodic limb movements during sleep (eg, hock dorsiflexion) have been described in dogs with narcolepsy.3,9

When narcolepsy signs are subtle and the episodes do not decrease the quality of life of a dog, treatment could be postponed.3 Tricyclic antidepressants (eg, imipramine hydrochloride) can be used to treat cataplexy because of their anticholinergic properties.3,5,10 Central nervous system stimulants (eg, methylphenidate or seleginine) can be administered mainly to treat excessive sleepiness.3,5 In dogs, α2-adrenergic receptor antagonists (eg, yohimbine),3,5 eugeroic drugs (eg, modafinil),11 and selective serotonin reuptake inhibitors (eg, fluoxetine) have had variable anticataplectic effects.10 Following IV administration, hypocretin-1 does not seem to penetrate the blood-brain barrier appropriately, and thus is not an effective treatment.5

In general, narcolepsy is nonprogressive and nonfatal, and affected dogs have a good prognosis with or without treatment; however, treatment should be considered when a dog’s quality of life is severely affected. The case described in the present report highlighted the importance of accurate interpretation of the clinical signs (particularly given that partial cataplexy can mimic any neuromuscular or cardiogenic collapse), with awareness and use of appropriate clinical or pharmacological provocative tests (eg, administration of physostigmine and food-elicited cataplexy testing) or preventive tests (eg, trial treatments with atropine, imipramine, or edrophonium) to identify the nature of the collapse episodes in dogs. Moreover, as indicated by this case, clinicians should remember that not only purebred dogs but also crossbreeds can develop primary narcolepsy, which may suggest a potential unknown hereditary basis of the disease in crossbred dogs as well.

**Footnotes**

a ELISA for antigen, SNAP Heartworm RT Test, IDEXX Laboratories, Wetherby, UK.

b MRI, 0.25T Signa Profile, General Electric Healthcare, Medical Systems, Athens, Greece

c Radioimmunoassay (RIA), Cambridge Specialist Laboratory Services, Cambridge, UK

d Radioimmunoassay (RIA), Center for Narcolepsy, Department of Psychiatry and Behavioral Sciences, School of Medicine, Stanford University, Stanford, CA

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**Figure 1.** Photographs of the 6-year old intact male crossbreed showing an episode of partial collapse of the pelvic limbs after exercise or excitement (A,B) and complete collapse after food intake (C-G).

**Supplementary Video.** Video of the 6-year-old intact male crossbreed dog showing the episodes of partial or complete collapse, the food-elicited cataplexy test and atropine suppression test. The final diagnosis for this dog was primary narcolepsy.