

Ataxic Gait in an English Bulldog

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Presentation

A 1.5-year-old, 53-lb (24.1-kg) spayed English bulldog was presented on emergency for evaluation following a sudden onset of abnormal gait. A few days prior, the dog showed weakness in the right pelvic limb, which progressed to both pelvic limbs the same day. The day before admission, the dog developed significant incoordination in all 4 limbs and had a spastic gait. The dog also had chronic GI disease that was being treated with metronidazole and a novel protein diet.

Physical Examination

The dog was bright, alert, and responsive but nervous and had a normal temperature of 101.9°F (38.8°C). She was tachycardic (160 bpm) and tachypneic (52 breaths/minute); this was attributed to anxiety and stress, as both parameters returned to

normal within 1 hour of admission without treatment. Cardiovascular and pulmonary auscultation were normal, and bilateral otitis externa was noted. Besides the neurologic examination (**Table 1**), the remainder of the physical examination was normal.

Treatment

Because of the history of metronidazole administration and the presence of vestibular dysfunction, the primary differential diagnosis was metronidazole toxicosis. The dog was admitted to the hospital for IV fluids and general supportive care, with the potential for advanced diagnostic testing, including an MRI and CSF tap, if the patient failed to improve or worsened. The clients confirmed that the patient had been receiving metronidazole (500 mg PO q12h [20.8 mg/kg PO q12h]) for the past 3 to 4 months.

Diagnosis

Metronidazole neurotoxicosis

Metronidazole is an antimicrobial, antiprotozoal, and anti-inflammatory drug with high bioavailability in most tissues, including the CNS.^{1,2} It is used to treat inflammatory bowel disease, giardiasis, and anaerobic infections.^{1,2} Reported side effects and adverse events in dogs and cats include vomiting, hepatotoxicity, neutropenia, and CNS signs.^{1,2} Clinical signs of neurotoxicity include seizures, mild-to-nonambulatory upper motor neuron paresis, central vestibular signs (eg, vertical nystagmus, head tilt, falling, vestibular ataxia), tremors, and rigidity.³⁻⁷ Cerebellar and vestibular signs are more common in dogs,^{3,4} whereas forebrain (cortical or thalamic) signs (eg, altered mental status, seizures, circling, pacing, behavior changes) are more common in cats.^{5,6}

The exact mechanism of action of neurotoxicity is unknown. Histologic examination of brain tissue from affected dogs shows Purkinje cell loss and axonal degeneration in vestibular tracts.³ It is possible that metronidazole directly damages these cells via an unknown mechanism. However, it has also been hypothesized that metronidazole binds to benzodiazepine receptor sites on gamma-aminobutyric acid (GABA) chloride channels of inhibitory interneurons in the cerebellum and central vestibular nuclei, preventing chloride conductance into these interneurons and leading to loss of inhibition and, in turn, increased excitation of cerebellar and vestibular nuclei.⁷ GABAergic receptors are also found in the olfactory bulbs, cuneate nuclei, lateral septal nuclei, hippocampus, trochlear motor neurons, and cerebral cortex and between the substantia nigra and caudate nucleus.^{8,9} Blockade of GABAergic receptors causes forebrain and other noncerebellar vestibular clinical signs.

TABLE 1

NEUROLOGIC EXAMINATION

(SEE VIDEO AT CLINICIANSBRIEF.COM/ATAXIC-GAIT-ENGLISH-BULLDOG)

Neurologic Examination	Findings
Mental status	Bright, alert, and responsive; nervous
Gait and posture	Ataxia with a tendency to lean and veer to the left, falling occasionally, stumbles when startled
Cranial nerves	Resting and positional vertical nystagmus, remainder normal
Postural reactions	Normal in all 4 limbs
Spinal nerve reflexes	Normal patellar bilaterally
Withdrawal	Normal in all 4 limbs
Palpation	No neck or back pain
Muscle tone	Normal in all 4 limbs
Muscle atrophy	None
Cutaneous trunci	Normal bilaterally
Nociception	Normal in all 4 limbs
Neurolocalization	Central vestibular dysfunction (left side worse than right)

Neurotoxicosis has been reported in dogs receiving metronidazole at >60 mg/kg q24h between 3 to 14 days of administration. Toxicity at lower doses also has been reported with chronic administration.³⁻⁶ In the largest study to date of metronidazole neurotoxicosis ($n = 21$ dogs), the average dosage reported was ≈ 60 mg/kg q24h but ranged from 33.3–110 mg/kg q24h.⁷ The dog in this case had been receiving a total daily dose of 41.6 mg/kg for several months.

GABA = gamma-aminobutyric acid

Diagnosis of metronidazole neurotoxicosis is based on history of a potentially toxic dosage of metronidazole combined with compatible clinical signs and improvement following discontinuation of metronidazole.

Treatment consists of immediate discontinuation of metronidazole. This alone should lead to resolution of clinical signs with an average recovery time (ie, time between treatment onset and full recovery) of 11 days.⁶ However, administration of diazepam (0.5 mg/kg IV bolus followed by 0.5 mg/kg PO q8h until resolution of signs) has been shown to shorten

the average response time (ie, time between treatment onset and initial signs of improvement) from 4.25 days (stopping metronidazole only) to 13.4 hours (with administration of diazepam) and shorten the average recovery time from 11 days to 38.8 hours.⁶ The mechanism by which diazepam facilitates recovery is uncertain, but diazepam has been proposed to have a higher affinity for the benzodiazepine site on the GABA channel, which allows it to dislodge the metronidazole from the receptor and restore normal chloride conductance and function of the inhibitory interneurons.⁶

The prognosis for full recovery is excellent. Avoiding future use of metronidazole is recommended; if administration is necessary, a dosage <30 mg/kg q24h is advised, as the lowest reported toxic dosage was 33 mg/kg q24h.⁶

TABLE 2

PERIPHERAL VS CENTRAL VESTIBULAR DYSFUNCTION*

Clinical Sign	Peripheral	Central
Loss of balance	Yes	Yes
Head tilt	Yes	Yes
Vestibular ataxia	Yes	Yes
Nystagmus		
Horizontal	Yes	Rare
Rotary	Yes	Yes
Vertical	No	Possible
Changing direction	No	Possible
Positional ventral strabismus	Yes	Yes
Cranial nerve deficits	Possible (VII only)	Possible (V-XII)
Horner Syndrome	Possible	Possible but rare
Cerebellar signs	No	Possible
Altered mental status	No	Possible
Postural reaction deficits	No	Typical

*Table adapted from one used in author's lectures and website (neuropetvet.com)

Treatment & Outcome

The dog was administered a single IV bolus of diazepam (0.5 mg/kg IV) followed by diazepam (10 mg PO q8h) until resolution of clinical signs. Diazepam was discontinued on day 5 after resolution of vestibular ataxia. Recheck neurologic examination 1 week later (see video at cliniciansbrief.com/ataxic-gait-english-bulldog) was within normal limits.

Discussion

Clinical signs observed during the neurologic examination can help differentiate central from peripheral vestibular dysfunction (Table 2).

Differential diagnoses include metronidazole neurotoxicosis, encephalitis (immune-mediated [eg, granulomatous meningoencephalomyelitis, necrotizing leukoencephalitis, idiopathic eosinophilic meningoencephalitis] or infectious [eg, canine distemper virus, rabies virus, *Cryptococcus neoformans*, *Ehrlichia canis*, *Rickettsia rickettsii*, *Anaplasma phagocytophilum*, *Borrelia burgdorferi*, *Neospora caninum*, *Toxoplasma gondii*]), bilateral otitis

interna with or without intracranial extension, neoplasia (eg, medulloblastoma), degenerative disease (eg, lysosomal storage disease), and congenital malformation.

The minimum database for patients with central vestibular dysfunction includes CBC, serum chemistry profile, urinalysis, thyroid hormone screening, and blood pressure measurement. Other diagnostics (eg, thoracic radiography, abdominal ultrasonography, infectious disease testing) can be considered as indicated. For patients with suspected metronidazole intoxication, diagnostics may not be necessary if response to treatment is good.

MRI is the imaging modality of choice for central vestibular dysfunction because it provides superior soft-tissue resolution and gives the clinician the ability to obtain all 3 imaging planes (ie, sagittal, transverse, dorsal) without moving the patient and without exposure to ionizing radiation. CT imaging provides less soft-tissue contrast, particularly around the brainstem and cerebellum, because of beam-hardening artifacts. ■

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GABA = gamma-aminobutyric acid

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