What Is Your Diagnosis?

In collaboration with the American College of Veterinary Radiology

Figure 1—T2-weighted (transverse [A], dorsal [B], and parasagittal [C] planes), FLAIR (transverse plane [D]), precontrast T1-weighted (transverse plane [E]), and postcontrast T1-weighted (transverse plane [F]) MRI images of the brain at the level of the cerebellar nuclei of a 3.25-year-old castrated male Dachshund with a 2-day history of progressive neurologic signs.

History

A 3.25-year-old 8-kg castrated male Dachshund was referred because of a 2-day history of progressive neurologic signs. Adopted as a puppy, the dog had a history of chronic intermittent soft feces but had been otherwise healthy until about 2 weeks before referral, when it developed sudden-onset vomiting and diarrhea and was taken to the referring

veterinarian. Radiographic examination at that time was reportedly unremarkable, and a 2-week course of metronidazole (31.3 mg/kg, PO, q 12 h) was prescribed. The dog improved but later again developed diarrhea 2 days and then vomiting 1 day before referral. Results of hematology, serum biochemical analyses, and thyroxine assessment performed at the primary veterinary clinic were reportedly within reference limits, except for a Hct of 62% (reference range, 36% to 60%). That night, the patient became ataxic and was vocalizing after a potential fall when he tried to run up the stairs. The next day, the referring veterinarian prescribed gabapentin (12.5 mg/kg, PO, q 8 h) and methocarbamol (15.6 mg/kg, PO, q 8 h). Overnight, the patient became unable to stand or walk on all 4 limbs and was referred for neurologic consultation.

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On referral examination, the dog was mildly hypothermic (37.1 °C; reference range, 37.9 to 39.9 °C) but had a clinically normal heart rate (100 beats/min; reference range, 70 to 120 beats/min) and respiratory rate (32 breaths/min; reference range, 18 to 34 breaths/min). The body weight was 8 kg (17.6 lbs), and the body condition score was 5/9. The remainder of the general physical examination was unremarkable. On neurologic examination, the dog was mentally dull and showed positional vertical nystagmus and an absent menace response oculus uterque. The remainder of the cranial nerve examination was normal. Truncal sway was noted at rest. The dog was weakly ambulatory with moderate to marked generalized vestibulocerebellar ataxia. Absent conscious proprioception was noted in all 4 limbs. While carrying his head low, the dog showed no signs of pain along the vertebral column. Spinal nerve reflexes and superficial pain sensation remained intact. Neurolocalization of central vestibular dysfunction was made.

The dog underwent general anesthesia, including IV fluid support, induction with fentanyl (0.005 mg/kg, IV) and propofol (5 mg/kg, IV), intubation, and maintenance with inhalant isoflurane (vaporizer setting, 1% to 2%) in oxygen (flow rate, 1 L/min), for MRI (Signa Excite 1.5T scanner, GE Healthcare). Images of the brain (**Figure 1**) were acquired with the patient in ventral recumbency in a knee coil,

and MRI sequences obtained included precontrast T1-weighted, postcontrast T1-weighted, T2-weighted, proton density, T2* gradient recalled echo, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted (DW) imaging as well as apparent diffusion coefficient (ADC) and exponential ADC maps. Post-contrast images were obtained after IV administration of gadodiamide (Omniscan, GE Healthcare; 287 mg gadodiamide/mL; 1.7 mL; 0.21 mL/kg).

Formulate differential diagnoses, then continue reading.

Diagnostic Imaging Findings and Interpretation

Bilaterally symmetric T2, FLAIR and T1 hyperintensity and subtle contrast enhancement of the dentate, interpositus, and fastigial cerebellar nuclei were present (**Figure 2**). The remaining findings on MRI were within reference limits. Based on these specific nuclei changes and the history, a diagnosis of metronidazole-induced neurotoxicity was made.

Treatment and Outcome

The MRI diagnosis was consistent with the clinical suggestion of drug-induced neurotoxicity based on the patient's history of metronidazole administration and central vestibular neurolocalization.

Figure 2—Same MR images as in Figure 1. The images show bilaterally symmetric hyperintense T2-weighted [A-C] and FLAIR [D] signals in the fastigial (long arrows) and interpositus and dentate (short arrows) nuclei in the cerebellar white matter. These same nuclei also show subtle contrast enhancement on the postcontrast T1-weighted transverse image (F) when compared to the precontrast T1-weighted transverse image (E). CdCP = Caudal cerebellar peduncle. CH = Cerebral hemisphere. CPs = Cerebellar peduncles. CV = Cerebellar vermis. T = Thalamus. TB = Tympanic bulla.

Treatment consisted of immediate cessation of metronidazole and administration of diazepam (0.4 mg/kg, IV as a bolus once, followed by 0.38 mg/kg, PO, q 8 h for 3 days), which has been shown to expedite recovery time in dogs with metronidazole toxicosis.¹ The patient showed progressive improvement after treatment initiation, with resolution of all neurologic signs within 3 days.

Comments

In dogs and cats, reported neurologic signs of metronidazole toxicosis include disorientation, head tilt, pathologic nystagmus, intentional tremors, forelimb and hind limb extensor rigidity, spastic paresis, hypermetria, ataxia, nonambulation, and seizures.¹⁻³ Relative to brainstem deficits, forebrain signs are more likely to be seen in cats.^{1,2} Neurotoxicity is most often reported in dogs given oral metronidazole dosages > 60 mg/kg/d but has also been shown to occur at lower daily dosages; therefore, caution is recommended when administering metronidazole to dogs at dosages > 40 mg/kg/d for any duration.³ The use of MRI enables clinicians to differentiate many intracranial or otic conditions in patients presenting with cerebellar, central vestibular, or forebrain dysfunction, such as cerebellar abiotrophy and vestibular infection.

Located bilaterally within the white matter, the cerebellar nuclei in dogs consist of the fastigial nucleus, interpositus nucleus, and lateral or dentate nucleus.⁴ Consistent with the MRI features for the dog of the present report, the most characteristic change in people with metronidazole neurotoxicity is symmetric hyperintensity of dentate nucleus on T2-weighted or FLAIR images, though it can also affect other intracranial sites, such as the midbrain, pons, medulla, and splenium of corpus callosum.^{5,6} Tauro et al³ reported non-contrast-enhancing, symmetric T2 and FLAIR hyperintensity of the dentate nuclei in a dog with metronidazole neurotoxicity. It is important to note that in that study,³ only 1 of the 19 dogs with clinically suspected metronidazole neurotoxicity that had MRI performed showed changes to the dentate nuclei, underscoring the possibility of

premature exclusion of a reversible condition based on normal imaging findings alone. A geriatric woman who continued metronidazole treatment for 24 days after onset of clinical signs and appearance of MRI lesions showed worsening of signs and imaging features, which progressed from the involvement of dentate nuclei, splenium, and periaqueductal midbrain to that of the cerebral white matter and brainstem,⁵ indicating potentially more diffuse lesions in progressive cases. Resolution of clinical signs and MRI lesions in most patients between 3 and 16 weeks after drug discontinuation has been reported in humans.⁵

In conclusion, metronidazole neurotoxicity is a cause of cerebellar and central vestibular deficits in dogs. Patient history, including previous or current gastrointestinal conditions and metronidazole administration, should alert the clinician to the possibility of metronidazole toxicosis. However, diseases of the cerebellum and the vestibular system should be considered based on clinical indication. The use of MRI can help differentiate many of these conditions, with metronidazole neurotoxicity having a characteristic MRI appearance that affects the dentate nucleus of the cerebellum or, as in the dog of the present report, the dentate, interpositus, and fastigial nuclei of the cerebellum. However, metronidazole neurotoxicity should not be excluded based on negative MRI findings.

References

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