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Case Report

Fatal caffeine intoxication in a dog

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Abstract

An 8-month-old male Yorkshire terrier was presented for ingestion of 800 mg of an over-the-counter caffeine supplement. Clinical signs included extreme tachycardia, facial fasciculation, coma/stupor and flailing. Due to the lack of response to medical therapies, humane euthanasia was elected. Microscopically, necrotic neurons were scattered throughout the hippocampus, olfactory cortex, pyriform lobe, amygdala, and basal nuclei, with relative sparing of the caudate nuclei. In addition, mild skeletal myocyte necrosis and mural necrosis of cardiac arterioles in the left and right ventricles were noted. This is the first report of the microscopic lesions associated with caffeine intoxication in a dog.

Key words: caffeine toxicity; neuron necrosis.

Introduction

Caffeine is a natural plant alkaloid found in more than 60 plant species and many beverage and food products, over the counter dietary supplements, and medications (9). Caffeine is the common name for the chemical 1,3,7-trimethylxanthine, which is absorbed through the gastrointestinal tract and metabolized by the liver (5, 9). Caffeine is generally considered a safe compound because it has a high threshold of toxicity and is a gastric irritant with emetic properties (20). Reports of toxicosis in the medical literature have been attributed to both accidental and intentional overdose (3, 4, 7, 14, 24, 25). The few case reports in dogs have been related to accidental ingestion or presumptive malicious poisoning (6, 12, 16, 22, 23). To the best of our knowledge, this is the first detailed description of the pathologic findings in canine caffeine intoxication.

Case report

An 8-month-old, male, 1.5 kg Yorkshire terrier presented to an emergency hospital with an acute onset of extreme tachycardia (HR = 220 bpm) after witnessed ingestion of 4 x 200 mg (800 mg) caffeine tablets between 6 to 8 hours previously, which is a dose of approximately 533 mg/kg. The only active ingredient in the over the counter caffeine supplement was caffeine. Due to rapid absorption of the toxin and presentation with clinical signs of cardiovascular and neurologic instability, gastric decontamination was deemed unsafe and therefore not performed. During hospitalization, the dog experienced 3 tonic seizures, which progressed to alternating periods of stupor/coma and flailing with facial fasciculation for the next 2 days. Tachycardia was moderately controlled with beta-blockers; however, the patient was refractory to pharmaceutical management of intracranial signs including cluster seizures, inappropriate mentation, and eventual display of intracranial hypertension as evidenced by a Cushing reflex. Serial bloodwork from 24 hours after ingestion and at 48 hours revealed progressively increasing aspartate aminotransferase (AST) 1124 U/L to 1768 U/L (10-34 U/L) and alanine aminotransferase (ALT) 217 U/L to 490 U/L (10-130 U/L). Creatine kinase (CK) remained > 16,000 U/L (68-400 U/L), and cardiac troponin was severely increased (3.306 ng/ml [0-0.06]). Urinalysis

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revealed myoglobinuria. The dog developed ptyalism, loss of gag reflex, possible aspiration pneumonia, and ultimately humane euthanasia was elected 2 days after ingestion of caffeine.

A complete necropsy was performed, and no gross lesions were observed. Sections of heart, kidney, liver, lung, pancreas, spleen, urinary bladder, thyroid gland, parathyroid gland, skeletal muscle, stomach, small intestine, colon, cerebrum, thalamus, hippocampus, cerebellum, midbrain, and medulla oblongata were fixed in 10% neutral buffered formalin, processed routinely, embedded in paraffin, and stained by hematoxylin and eosin (HE) for light microscopy. Due to the witnessed ingestion of caffeine supplements and the lack of exposure to any other toxin, blood or tissue were not assessed for caffeine levels in this case.

Microscopic brain lesions were largely limited to the telencephalon and diencephalon. Scattered areas of neuronal necrosis, varying from minimal to severe, were evident throughout all cerebral lobes. Necrotic neurons were shrunken and angular with hypereosinophilic cytoplasm and pyknotic nuclei. Necrosis was severe in the hippocampus, olfactory cortex, pyriform lobe, amygdala, and basal nuclei, with relative sparing of the caudate nuclei. Both the pyramidal layer (CA1-CA4) and dentate layer of the hippocampus were severely and diffusely affected (Fig. 1). In the cerebral cortex, necrotic neurons were evident in superficial, middle, and deep layers without a clear laminar pattern. Necrotic neurons and occasional swollen axons (spheroids) were evident in the thalamus, most notably in the lateral geniculate nucleus (Fig. 2). The dorsal thalamus was more affected than the ventral thalamus. A few necrotic neurons had multiple basophilic incrustations along their cell membrane (Fig. 2, inset). Necrotic neurons and adjacent blood vessels were often surrounded by clear space interpreted as cytotoxic edema (Fig. 3). Other vessel changes in affected areas included hypertrophy of endothelial cells and occasional mitotic figures. Rare Purkinje cell necrosis was seen in the cerebellum. The midbrain and medulla oblongata were within normal limits. Additional microscopic findings of this case included scattered necrotic skeletal myocytes and mural necrosis of arterioles and small arteries in the left and right ventricles (Fig. 4).

Discussion

The toxic dose of caffeine for dogs is reported to be 140-150 mg/kg (20). The diagnosis of caffeine intoxication in humans is often based on history of caffeine ingestion with corresponding caffeine levels in blood or tissue samples (4, 7, 14, 25). In this case, caffeine levels were not evaluated, but a presumptive diagnosis of caffeine intoxication was made based on the history. Reported pathologic findings in human cases of caffeine intoxication include pulmonary edema, visceral congestion, myocardial infarction, rhabdomyolysis, and mild gastric erosion with hemorrhage (4, 7, 24, 25). Lesions in the central nervous system are limited to cerebral edema, although most reports do not include brain histology (25). The pathology of caffeine toxicosis in dogs is poorly characterized. Necropsies were not performed in most of the reported cases nor were caffeine levels in the blood or tissues evaluated (12, 16, 19, 23). Two cases that received necropsies reported no gross findings, and histopathology was not done in either case (6, 22).

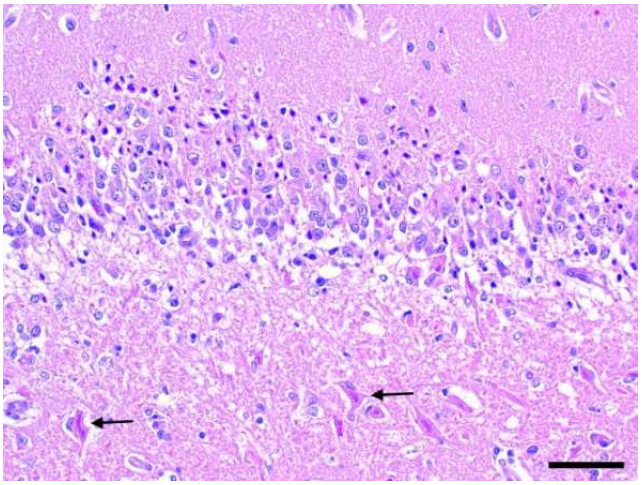


Figure 1. Hippocampus. Hypereosinophilic and shrunken neurons in the dentate layer and within the pyramidal layer (arrows). HE. Bar, 70 µm.

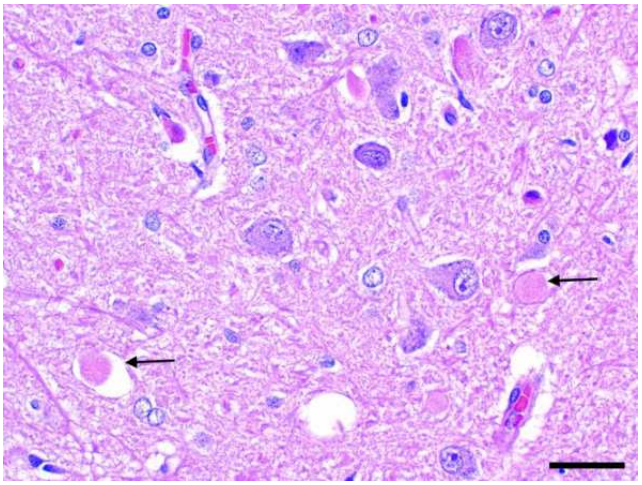


Figure 2. Thalamus. Multifocal swollen axons (arrows) in the lateral geniculate nucleus. HE. Bar, 35 µm.

While caffeine intoxication is the most likely diagnosis, similar microscopic lesions have been attributed to seizure activity in epileptic dogs and are also seen in dogs with cardiac arrest, cranial trauma, and hypoglycemia (11, 13, 17, 18). The dog did not have a previous history of epilepsy and lacked gross lesions or a history of cranial trauma. In a study of epileptic beagles, the distribution and nature of the lesions was similar to this case, involving the cerebral cortex, basal nuclei, claustrum, amygdala, septal

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nuclei, dorsal thalamic nuclei, isthmus of the pyriform lobe, and hippocampus (13). The rostral cerebrum was most severely affected, specifically the medial aspect of the frontal lobes and the cingulate gyrus, a finding not appreciated in this case. The beagles had infrequent cerebellar Purkinje cell necrosis, neuronal necrosis in the thalamus, and frequent neuronal incrustation, all similar to this case. Incrustations are a change that has been attributed to dense pockets of neuronal cytoplasm caused by impingement of swollen astrocyte processes on the neuronal cell membrane (21). Hippocampal necrosis was seen in CA1-CA4 in the beagle study, but did not involve the dentate gyrus, as it did in this case. Another change not mentioned in the epileptic beagles but seen in this case is the presence of spheroids within the thalamus, particularly the lateral geniculate nucleus.

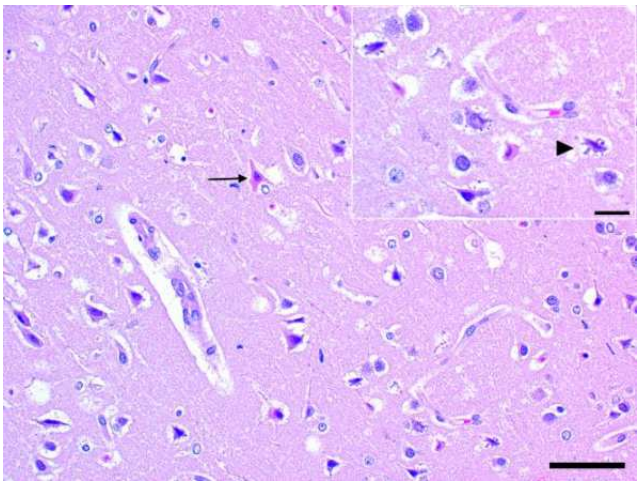


Figure 3. Cerebrum. The perivascular space is expanded by clear space interpreted as edema. Multifocally, neurons are necrotic (arrow). HE. Bar, 70 µm. Upper inset. Some neurons have basophilic incrustations along the cell membrane (arrow head). HE. Bar, 20 µm.

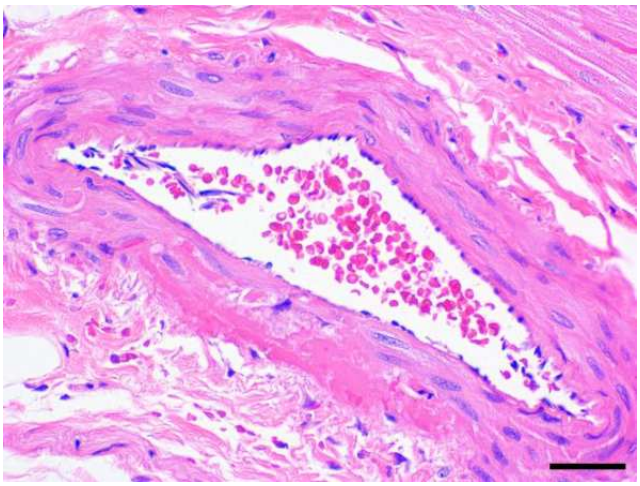


Figure 4. Heart. Mural fibrinoid necrosis in an epicardial small artery. HE. Bar, 20 µm.

The prominent histologic findings of neuronal necrosis and cytotoxic edema could be entirely due to seizure activity or hypoxia resulting from cardiovascular collapse, rather than from any direct toxic effects of caffeine. Caffeine increases the rate of metabolism of structures within the extrapyramidal motor system, thalamic nuclei, and hippocampus, resulting in relative hypoperfusion of these areas (15). Caffeine also causes transient vasoconstriction, which could contribute to relative hypoperfusion (15). The lesions in this dog could be secondary to the inherent vasoconstrictive properties of caffeine and increased glucose utilization within the central nervous system.

Diffuse brain hypoxia from cardiopulmonary dysfunction is another possible explanation for the brain lesions. Myocardial infarction and cardiac arrest have been reported after massive ingestion of caffeine in the medical literature, resulting in abnormal electrocardiograph (ECG) findings and elevated cardiac troponin levels (3, 7). Cardiac arrest with resulting global ischemia is a well-known cause of neurologic deficits. In a research model utilizing pigs, cardiac arrest of 7 or 10 minutes duration resulted in varying degrees of neuronal necrosis and cerebral edema within the cerebral cortex, caudate nucleus, putamen, hippocampus, thalamus, and cerebellar median fissure (10). Necrotic neurons were found in layers III and V of the 7 minute group and progressed to diffuse involvement by 10 minutes. The lesions reported in these pigs are similar to those described in this case. The dog did not experience cardiac arrest, but elevated cardiac troponin and mural necrosis of epicardial arterioles of the left and right ventricles suggests compromised myocardial function. Vascular necrosis has apparently not been observed in previous cases of canine or human caffeine toxicity.

Caffeine is quickly absorbed after ingestion and reaches peak serum levels within 1 hour (2, 20). Clinical signs include gastrointestinal derangements (vomiting, diarrhea), cardiovascular instability (hypertension or hypotension, tachycardia), and neurologic effects (delusions, hallucinations, and seizures) (14, 20). Caffeine's effects are mediated through competitive antagonism of adenosine receptors, which are found in the cardiovascular, respiratory, renal, gastrointestinal, and central nervous systems (1, 2).

Caffeine is a potent stimulant. Although toxicity is rare in dogs, the drug can induce severe pathologic changes in the species. The extent to which the lesions reported herein are due to seizure activity, cardiopulmonary dysfunction, or some other mechanism remains to be determined.

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