Diagnosis of presumed acute ischemic stroke and associated seizure management in a Congo African grey parrot

Hugues Beaufrère, Dr Med Vet; Javier Nevarez, DVM, PhD; Lorrie Gaschen, DVM, PhD; Kirk Ryan, DVM, DACVIM; Rodney Schnellbacher, DVM; Thomas Tully, DVM, MS, DABVP

Case Description—A 14-year-old Congo African grey parrot (Psittacus erithacus erithacus) was evaluated for an acute onset of falling off of its perch and tonic- clonic movements.

Clinical Findings—Clinical signs were consistent with partial seizures. Findings on whole- body radiography, CBC, and plasma biochemical analysis were unremarkable. Plasma magnesium, ionized calcium, and bile acids concentrations were within reference limits. A magnetic resonance imaging (MRI) examination of the head revealed the presence of a focal hyperintensity at the central to left side of the optic chiasm and a hyperintense focus in the right side of the midbrain area in T2-weighted and FLAIR pulse sequence images. These findings were most consistent with an acute ischemic stroke with 2 brain infarcts.

Treatment and Outcome—Seizures were initially managed with potassium bromide and phenobarbital administration. On the basis of poor results and difficulties to reach therapeutic blood concentrations, the treatment plan was changed to levetiracetam and zonisamide administration. Blood concentrations were monitored for both drugs, and the frequency of seizures substantially decreased thereafter. A follow-up MRI examination 2 months later revealed resolution of the hyperintense signals. During the 20-month follow-up period, subsequent clusters of seizures were managed by adjusting levetiracetam and zonisamide dosages and adding clonazepam and gabapentin administration to the treatment plan. Regression of intraparenchymal hyperintense lesions and improvement of clinical signs made a diagnosis of acute ischemic stroke most likely.

Clinical Relevance—Findings for this Congo African grey parrot indicated that an antemortem diagnosis of an acute ischemic stroke followed by long-term seizure management may be possible in affected psittacines. (J Am Vet Med Assoc 2011;239:122–128)

ABBREVIATIONS

<table>
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<tr>
<th>FLAIR</th>
<th>Fluid-attenuated inversion recovery</th>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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A 14-year-old female Congo African grey parrot was evaluated on an emergency basis at the Louisiana State University Veterinary Teaching Hospital for acute onset of repeated falling off of its perch, shaking, lethargy, and spastic motions. The bird was fed a seed-based diet occasionally supplemented with table food. The owner acquired the bird when it was a chick and possessed 3 other parrots that were healthy. The owner reported that when the bird fell off of its perch, it would extend its left pelvic limb, grab the cage with its right pelvic limb, and vocalize, and it had questionable vision in its left eye. Upon examination, the parrot appeared weak and had poor balance. A blood sample was taken from the right jugular vein and submitted for CBC, plasma biochemical analysis, and determination of plasma bile acids and magnesium concentrations. Findings on CBC and plasma biochemical analysis were unremarkable. Plasma total calcium concentration was within reference range limits (2.1 mmol/L; reference range, 2.1 to 2.6 mmol/L). Blood ionized calcium concentration was obtained by use of a portable blood analyzer, and the value was within reference range limits (1.07 mmol/L; reference range, 0.96 to 1.22 mmol/L). Plasma magnesium concentration was also within reference range limits (2.1 mg/dL; reference range, 2.0 to 2.6 mg/dL). Apart from the weakness and the poor balance, no further neurologic signs were noted on the day of hospital admission. The bird was initially given calcium gluconate (100 mg/kg [43.5 mg/lb], SC), lactated Ringer’s solution (50 mL/kg [22.7 mL/lb], SC), and magnesium sulfate (20 mg/kg [9.1 mg/lb], IM). The following day, the bird was anesthetized with isoflurane and whole-body radiographs were obtained. No radiographic abnormalities were observed. While the bird was under anesthesia, a fundic examination was performed with a direct ophthalmoscope and did not reveal any abnormalities. The bird had a delayed recovery from anesthesia and had difficulties standing and perching. It subsequently had an episode of seizures characterized by lateral recumbency, opisthotonos, a slight head tilt to the left, pronation of the feet, hypertonicity of its left pelvic limb, and an apparent loss of vision in the left eye (Figure 1). These neurologic signs were compatible with a right-sided CNS lesion. Diazepam was administered (1 mg/kg [0.5 mg/lb], IM), and the neurologic signs resolved. Approximately 2 hours later, the parrot had another episode of seizures.
with voiding of feces and diazepam administration was repeated, but at a higher dose (2 mg/kg [0.9 mg/lb], IM). The signs resolved, but the bird appeared imbalanced and had a poor perching ability.

To further investigate the etiology of the seizure activity, an MRI examination of the brain was planned for the following day. The bird was premedicated with midazolam (0.2 mg/kg [0.09 mg/lb], IM) and butorphanol (2 mg/kg, IM) administration, and was mask induced with 5% isoflurane. The bird was then intubated and maintained under anesthesia with 1% to 3% isoflurane and oxygen (1 L/min) administration during the entire procedure. A catheter was placed in the medial metatarsal vein for contrast administration. During MRI, the bird's body temperature was maintained with bags of warmed rice placed on each side of the bird and cellophane sheets placed over its body. Anesthesia was monitored with an MRI-compatible stethoscope and ECG. The bird's head was placed in an MRI surface coil designed to image human knee joints, and the following MRI pulse sequences were obtained: sagittal T2 weighted, dorsal T2 weighted, transverse T2 weighted, T1 weighted, FLAIR, and T2* weighted. Additionally, gadolinium at 0.1 mmol/kg (0.05 mmol/lb) was administered IV, and a postcontrast transverse T1-weighted sequence was performed. Magnetic resonance imaging revealed the presence of a focal hyperintensity at the central to left side of the optic chiasm, which was ill-defined on T2-weighted images and also hyperintense on FLAIR images (Figure 2). At the midbrain, there was an ill-defined, hyperintense focus on the right side, which was hyperintense on T2-weighted and FLAIR images and isointense on the T1-weighted image (Figure 3). Contrast enhancement of the lesions was not observed. The anesthesia lasted for 1 hour and 30 minutes, and the bird recovered uneventfully. These MRI findings were compatible with an acute ischemic stroke with 2 brain infarcts. An inflammatory lesion was considered part of the differential diagnosis. Neoplasia was considered less likely because of the lack of contrast enhancement. Because of the asymmetric appearance of the signal intensities in the brain tissue and multifocal nature, an artifact was also considered less likely. The lesion locations were also compatible with the neurologic localization. By comparison with the budgerigar brain atlas, the lesions were determined to affect the left aspect of the optic chiasm and right side of the intermediate nidopallium, arcopallium, lateral striatum, and dorsomedial nucleus of the thalamus.

The bird began receiving potassium bromide (20 mg/kg, PO, q 12 h) and phenobarbital (2 mg/kg, PO, q 12 h). Dexamethasone sodium phosphate was administered (1 mg/kg, IM), and the same dose was given again the following day to address presumptive cerebral edema. Because of the onset of moderate to severe polyuria, dexamethasone treatment was subsequently discontinued. Considering the reported adverse effects of corticosteroids in psittacines and the relative frequency of aspergillosis...
in African grey parrots, the bird preformatively received voriconazole (5 mg/kg [2.3 mg/lb], PO, q 12 h) and enrofloxacin (10 mg/kg [4.5 mg/lb], PO, q 12 h). It was also gavage fed a hand-feeding formula (30 mL/kg [13.6 mL/lb], q 12 h) and received lactated Ringer’s solution (50 mL/kg/d, SC) for 2 days. Three days after initial examination, the bird started to have signs of restored vision in the left eye. To prevent further embolic events, the bird was also given acetylsalicylic acid (5 mg/kg, PO, q 48 h). Indirect arterial blood pressure, measured with a cuff around the humeral area and a Doppler unit with the pulse obtained from the deep radial artery on the carpus, was estimated as 200 mm Hg (reference range, 104 to 197 mm Hg for direct systolic blood pressure in Hispaniolan Amazon parrots). 6

The following day, the parrot had another seizure that resolved with administration of diazepam (1 mg/kg, IM). The potassium bromide dosage was increased (50 mg/kg, q 12 h), and the phenobarbital dosage was maintained (2 mg/kg, q 12 h). The bird did not have any subsequent seizures and was discharged 6 days after admission with instructions to the owner to administer potassium bromide (30 mg/kg, PO, q 12 h), phenobarbital (2 mg/kg, PO, q 12 h), acetylsalicylic acid (5 mg/kg, PO, q 48 h), enrofloxacin (10 mg/kg, PO, q 12 h for 1 week), and voriconazole (5 mg/kg, PO, q 12 h for 1 week). It was also recommended to change the bird’s diet to pellets supplemented with fresh fruits and vegetables and to limit the amount of seeds and table food in its diet.

The bird returned 3 weeks later for reevaluation and further diagnostic tests. The owner did not report any difficulties in giving the medications, and the bird’s diet was then changed to approximately 80% pellets. No evidence of sedation or adverse effects of the medications were noticed. The owner reported approximately 1 to 2 seizures/wk and also infrequently noticed a preictal behavior of the bird going to the bottom of the cage before a seizure. Postictal weakness and imbalance were also noticed for a few hours afterward. The parrot was given midazolam (0.2 mg/kg, IM) and manually restrained for transcoelomic echocardiography. Echocardiography did not reveal any abnormalities. The right ventricle, left ventricle, and aortic morphometric measurements were within reference range limits published for the species. 7 Considering the reported low reliability of indirect blood pressure measurement in psittacines, a direct arterial blood pressure measurement was attempted but the placement of an arterial catheter in the superficial ulnar artery was unsuccessful. A blood sample was taken from the right jugular vein and submitted to the Louisiana Animal Diagnostic Laboratory for trough serum phenobarbital and potassium bromide concentrations. The blood sample was obtained approximately 8 hours after the last treatment administered by the owner. Phenobarbital was not detectable in the blood with a concentration below 1 µg/mL (therapeutic range in dogs, 20 to 35 µg/mL). 8 Potassium bromide concentration was 0.6 mg/mL (therapeutic range in dogs, 1 to 3 mg/mL). 8 Considering these results, phenobarbital administration was discontinued and the potassium bromide dosage was increased (100 mg/kg, PO, q 12 h); additionally, a loading dose of potassium bromide (80 mg/kg [36.4 mg/lb], PO, q 12 h) was administered for 3 days (500 mg/kg total).

The bird was reevaluated 2 weeks later (3 weeks after initial examination), and the owner reported 2 additional seizures. Trough potassium bromide blood concentration was 0.7 µg/mL at this time. Considering the high frequency of seizures and the difficulties in controlling them with potassium bromide alone, levetiracetam (30 mg/kg [13.6 mg/lb], PO, q 12 h) was added to the therapeutic regimen. The dosage of potassium bromide was also increased (200 mg/kg [90.9 mg/lb], PO, q 12 h).

One week later (6 weeks after initial examination), the bird had another seizure at home. The bird appeared clinically normal at all other times, with no neurologic abnormalities or vision loss. The levetiracetam dose was increased (50 mg/kg, PO, q 12 h), and a loading dose of potassium bromide (80 mg/kg, PO, q 12 h) was administered for 3 days.

Two weeks after starting levetiracetam administration (8 weeks after initial examination), the bird was...
re evaluated. The owner reported the bird had 1 seizure at home. Blood samples were obtained to determine peak and trough serum levetiracetam concentrations and trough serum potassium bromide concentration; CBC and plasma biochemical analysis was performed. Findings on CBC and plasma biochemical analysis were unremarkable, including plasma calcium, bile acids, cholesterol, and triglycerides concentrations. Peak serum levetiracetam concentration was 12.5 µg/mL at 2 hours after the last oral dose was given (therapeutic range in humans, 3.5 to 21 µg/mL); trough serum levetiracetam concentration was 1 µg/mL at 12 hours after the last oral dose was given. The predicted half-life was determined as 3.3 hours. The trough serum potassium bromide blood concentration was unchanged at 0.7 mg/mL. On the basis of these results and the difficulties in adequately controlling the seizures, frequency of levetiracetam administration was increased to 3 times/d and zonisamide's predicted half-life, 8.6 hours). Given that the frequency of seizures was still considered too high, clonazepam administration (0.5 mg/kg [0.23 mg/lb], PO, q 12 h) was added to the therapeutic regimen. The bird's seizure frequency considerably decreased thereafter, with approximately 3 seizures in a 7-month period. Seven months after clonazepam administration was added (11 months after initial diagnosis), the bird started having a seizure every 3 weeks. The bird was hospitalized for 2 weeks, during which it had 2 seizures. It was weaned off the clonazepam, as the parrot was considered to have developed tolerance to it. The levetiracetam dose was doubled (100 mg/kg, PO, q 8 h), and gabapentin (20 mg/kg, PO, q 12 h) was added to the therapeutic regimen. One week later, the levetiracetam and zonisamide blood concentrations were reassessed and found to be higher than the previous concentrations (levetiracetam's peak at 2 hours after administration, 31.7 µg/mL; levetiracetam's trough at 9 hours after administration, 16.9 µg/mL; zonisamide's predicted half-life, 6.6 hours; zonisamide's peak at 2 hours after administration, 31.1 µg/mL; zonisamide's trough at 9 hours after administration, 21.8 µg/mL; zonisamide's predicted half-life, 11.7 hours). The bird had only 1 seizure over the 9-month period after the treatment was adjusted. During the 20-month follow-up, no adverse effects from any of the medications were noticed.

Discussion

In this clinical report, we describe the diagnosis of a presumed acute ischemic stroke in a Congo African grey parrot. We also report the management of the bird's seizure activity until adequately controlled. Magnetic resonance imaging was invaluable in detecting brain parenchymal lesions that corresponded to the neurologic localization and for follow-up after treatment. The abrupt onset of neurologic deficits coupled with detection of brain lesions by use of MRI, followed by resolution of these lesions 2 months later, is highly suggestive of an ischemic event in the brain. The partial nature of the seizures suggested a focal brain lesion. An encephalitis is considered less likely in view of the clinical improvement, the absence of inflammatory response on the CBC, and the fact that infectious and verminous encephalitis have a guarded to poor prognosis in pet birds (eg, proventricular dilation disease, West Nile virus, avian paramyxovirus, avian influenza, Baylisascaris procyonis, and Sarcocystis spp infections). However, specific diagnostic tests to rule out these differentials diagnoses were not performed. A blood lead concentration was also not obtained because the bird appeared clinically normal between seizures. Similarly, the bird was not tested for chlamydiosis. Nevertheless, without histologic examination of brain tissue, we could not confirm the diagnosis of stroke. The distribution of the lesions suggested at least 2 ischemic infarctions: 1 on the right side of the midbrain (intermediate nidopallium, aracopallium, lateral striatum, and dorsal medial nucleus of the thalamus) and 1 on the left part of the optical chiasm. Theoretically, an acute infarct should produce a bright MRI signal, reflect-
ing the increase in water content, mainly in the form of cytotoxic edema, on conventional T2-weighted and FLAIR images. Cytotoxic edema results from abnormal accumulation of intracellular water in ischemic brain tissue as a consequence of decreased availability of ATP and the resulting dysfunction of the Na-K-ATP pump. Absence of the bright signals at the 2-month follow-up MRI examination likely represents resolution of the edema secondary to infarction.

Acute ischemic stroke, also known as cerebrovascular accident and brain infarction, does not seem uncommon in psittacines, especially budgerigars and African grey parrots[10-12]. However, we were unable to find a single published clinical report with antemortem diagnosis and management. Cerebral hemorrhage with an ischemic lesion was suspected in an 85-year-old yellow-naped Amazon parrot (Amazona auropalliata) on the basis of computed tomographic findings and was later confirmed on histologic examination. In humans, acute ischemic strokes are caused by emboli, and the etiology includes systemic hypertension, cardioembolism, and atherosclerosis. Causes are likely similar in pet psittacines, for which a high incidence of atherosclerosis is reported. Additionally, yolk emboli may be another cause in female birds. Nevertheless, in humans, approximately 30% of strokes remain unexplained. In the bird of the present report, findings on transcoelomic echocardiography were unreleasable, measurement of direct arterial blood pressure was attempted but unsuccessful, and indirect methods to measure arterial blood pressure were considered unreliable. Atherosclerosis lesions were suspected on the basis of species, age, and diet, but given that the antemortem diagnosis of atherosclerosis is challenging, we could not confirm this suspicion.

Treatment of acute ischemic strokes in humans is divided into the early management that aims to prevent or reverse brain injury, the treatment of acute neurologic complications, and the prevention of recurrence. In light of the considerable amount of research and data available in the human literature, special guidelines for the early management of acute ischemic stroke have been published by the Stroke Council of the American Heart Association. The guidelines are based on strengths of recommendation, which are established by the strength of evidence gathered from randomized trials, cohort studies, and case series. Current recommendations include IV thrombolysis by use of recombinant tissue plasminogen activator within 3 hours of onset of a stroke in selected patients and administration of acetylsalicylic acid, an antiplatelet aggregating agent, within 48 hours. Other treatments that may be beneficial, but for which evidence is not strong enough or is conflicting, include anticoagulants such as low-molecular-weight heparin, drug-induced hypertension to improve cerebral blood flow, mechanical thrombolytic methods such as surgery and endovascular procedures, and neuroprotective agents. Acute neurologic complications such as brain edema, increased intracranial pressure, seizures, and hemorrhagic transformation should also be addressed. While corticosteroids are occasionally used to treat embolic event and brain infarction in veterinary medicine, their use is not recommended and may be contraindicated in humans as stated in the guidelines. The use of conventional or large doses of corticosteroids did not improve the outcomes after stroke, and infections were more common among patients treated with these drugs. Dexmethasone sodium phosphate was used in the bird of the present report for its potential beneficial effects in brain edema; however, in retrospect, the justification for its use is controversial. The management of this bird mainly consisted of supportive care, treatment of clinical seizure activity, and attempt at early prevention of recurrence with acetylsalicylic acid.

A variety of neurologic conditions have been reported to cause seizures in pet psittacines. The most common causes of seizures include heavy metal toxicosis, hypocalcemic syndrome of African grey parrots, hydrocephalus, infectious encephalitis (including proventricular dilation disease), hepatic encephalopathy, hypovitaminosis E, and hypoglycemia. Idiopathic epilepsy has also been reported in red-lored Amazon parrots (Amazona amazonica) and lovebirds. Interestingly, atherosclerosis has been reported to induce cerebral ischemia, leading to seizures and neurologic signs in parrots. In most clinically affected parrots, seizures were treated only in the short-term with diazepam or phenobarbital until resolution of the causative disease or death of the patient. The long-term treatment of seizures has been poorly described for parrots, and no clinical report could be found in the peer-reviewed literature. In the bird of the present report, phenobarbital and potassium bromide were ineffective at controlling seizures, and blood concentrations that are considered therapeutic for mammals could not be readily achieved. The use of potassium bromide, levetiracetam, zonisamide, clonazepam, and gabapentin for seizure management in birds has not been reported in the peer-reviewed literature. Substantial reduction in the frequency of seizures was observed when levetiracetam, zonisamide, clonazepam, and gabapentin were used for treatment of the bird in the present report. Furthermore, monitoring of blood drug concentrations in this parrot suggests that levetiracetam and zonisamide may be well absorbed in African grey parrots and achieve concentrations considered therapeutic in humans. Although the diminishing seizure frequency may have been caused by resolution of the brain edema and healing of the infarcted brain areas, the bird substantially improved once levetiracetam administration was started, and the subsequent clusters of seizures suggested that the lesions were still epileptogenic several months after the insult. The difficulties in achieving adequate blood concentrations of potassium bromide and phenobarbital in this bird, despite good owner compliance, are likely due to either a poor oral bioavailability or short half-lives of these drugs. This is surprising, considering the good bioavailability and extended half-life of these 2 drugs in mammals.

Potassium bromide is administered at 20 to 40 mg/kg (9.09 to 18.18 mg/lb) in dogs and has a reported half-life of 24 days, and steady-state kinetics are not reached until 80 to 120 days with the maintenance dose. Loading doses are usually used to attain steady-state kinetics sooner. In the bird of the present report, 2
loading doses were used in addition to a high-maintenance dose. However, the last potassium bromide blood concentration, 2 months after initiation of treatment, was still below concentrations reported therapeutic in mammals. In another clinical report, an Umbrella cockatoo (Cacatua alba) with seizures of undetermined origin was treated successfully with potassium bromide (80 mg/kg [36.4 mg/lb], PO, q 24 h) for 1 year, with serum concentrations ranging from 1.1 to 2.2 mg/mL. These findings suggest interspecies variation in the pharmacokinetics of potassium bromide in birds.

Phenobarbital is administered at 1 to 5 mg/kg in dogs and cats, has a half-life of 40 to 90 hours, and takes approximately 10 to 15 days to reach steady-state kinetics. Phenobarbital could not be detected in the blood of our parrot 3 weeks after initiation of treatment when administered at 2 mg/kg, PO, every 12 hours. In African grey parrots, a few reports when administered at 2 mg/kg, PO, every 12 hours.

Blood of our parrot 3 weeks after initiation of treatment mide and phenobarbital.

Phenobarbital administration was reported to be effective in controlling seizure activity in Amazon parrots at a dose of 2 to 5 mg/kg.

Levetiracetam and zonisamide have a short half-life in mammals of approximately 4 and 15 hours, respectively. These 2 drugs have good efficacy and have a high margin of safety in dogs, compared with potassium bromide and phenobarbital. Findings for the parrot of the present report indicate that these drugs may also be safe and effective in psittacines. An important drawback of the use of levetiracetam and zonisamide in parrots may be the required high frequency of administration, 2 to 3 times/d. Clonazepam is a benzodiazepine used to treat clusters of seizures and status epilepticus in mammals, but its use is associated with the rapid development of tolerance. It was found to be an effective addition for the parrot of the present report to treat clusters of seizures not entirely managed by levetiracetam and zonisamide. However, the bird seemed to develop tolerance approximately 7 months afterwards, and the use of clonazepam was discontinued. Gabapentin, a γ-aminobutyric acid analogue, is occasionally used as an adjunct treatment for dogs. This drug was also used as an adjunct treatment for the parrot of the present report when it started having more frequent seizures. As the bird was on an anticonvulsant multidrug treatment regimen, the characterization of the individual drugs effects may be hard to determine.

This clinical report illustrates the challenges associated with the diagnosis of an acute ischemic stroke in a parrot and the long-term management of its secondary seizure activity. It also emphasizes the need for more research in pharmacology of anticonvulsant medications and more clinical reports documenting their use in parrots.

References


From this month’s AJVR

Pharmacokinetics of tramadol and metabolites O-desmethyltramadol and N-desmethyltramadol in adult horses

Allison J. Stewart et al

Objective—To determine the pharmacokinetics of tramadol and its metabolites O-desmethyltramadol (ODT) and N-desmethyltramadol (NDT) in adult horses.

Animals—12 mixed-breed horses.

Procedures—Horses received tramadol IV (5 mg/kg, over 3 minutes) and orally (10 mg/kg) with a 6-day washout period in a randomized crossover design. Serum samples were collected over 48 hours. Serum tramadol, ODT, and NDT concentrations were measured via high-performance liquid chromatography and analyzed via noncompartmental analysis.

Results—Maximum mean ± SEM serum concentrations after IV administration for tramadol, ODT, and NDT were 5,027 ± 638 ng/mL, 0 ng/mL, and 73.7 ± 12.9 ng/mL, respectively. For tramadol, half-life, volume of distribution, area under the curve, and total body clearance after IV administration were 2.55 ± 0.88 hours, 4.02 ± 1.35 L/kg, 2,701 ± 275 h•ng/mL, and 30.1 ± 2.56 mL/min/kg, respectively. Maximal serum concentrations after oral administration for tramadol, ODT, and NDT were 238 ± 41.3 ng/mL, 86.8 ± 17.8 ng/mL, and 159 ± 20.4 ng/mL, respectively. After oral administration, half-life for tramadol, ODT, and NDT was 2.14 ± 0.50 hours, 1.01 ± 0.15 hours, and 2.62 ± 0.49 hours, respectively. Bioavailability of tramadol was 9.50 ± 1.28%. After oral administration, concentrations achieved minimum therapeutic ranges for humans for tramadol (> 100 ng/mL) and ODT (> 10 ng/mL) for 2.2 ± 0.46 hours and 2.04 ± 0.30 hours, respectively.

Conclusions and Clinical Relevance—Duration of analgesia after oral administration of tramadol might be < 3 hours in horses, with ODT and the parent compound contributing equally. (Am J Vet Res 2011;72:967–974)