Epilepsy is a disorder of the brain characterized by a predisposition to generate seizures and is the most common neurologic disorder found in dogs.\(^1\) The term is limited to seizures that result from an intracranial cause and is only applied to patients that have ≥ 1 seizure and a likelihood of future seizures.\(^2\) The International League Against Epilepsy has defined categories of seizures according to their etiology:\(^3\)\(^4\) Idiopathic, or primary, epilepsy is a recurrent seizure disorder without any known cause and no interictal deficits.\(^3\)\(^4\) The seizures are caused by molecular or microscopic abnormalities\(^5\)\(^6\) that cannot be detected with common diagnostic techniques and often have a genetic predisposition.\(^4\)\(^6\) Secondary or symptomatic epilepsy is a result of structural brain disease.\(^6\)\(^7\) Cryptogenic epilepsy, also known as probable symptomatic epilepsy, is defined as seizures that are suspected to be caused by pathological structural brain changes with no lesions detectable through complete diagnostic evaluation.\(^1\)\(^2\) Finally, reactive epilepsy is a response in the brain to systemic alterations, such as electrolyte derangements, uremia, or abnormalities resulting from hepatic disease, anesthesia-related events, or toxin exposure.\(^7\)\(^8\)

Most dogs with seizures have primary epilepsy.\(^9\)\(^10\) In veterinary medicine, there is an anecdotal impression that dogs ≥ 5 years of age that develop epilepsy most likely have intracranial lesions,\(^1\)\(^2\) and advanced diagnostic methods such as MRI and CSF analysis are strongly recommended in evaluation of these patients.\(^1\)\(^2\) Although primary epilepsy is thought to develop less commonly in dogs after 5 years of age,\(^1\)\(^2\) to our knowledge, the proportion of dogs in this category that have seizures without structural brain disease has not been reported. Therefore, the purpose of the study reported here was to classify the etiology of epilepsy in dogs ≥ 5 years of age, assess differences in type (primary or secondary) and etiology (neoplasia or other disease) of epilepsy among dogs stratified by age, and evaluate use of abnormal neurologic examination findings to predict secondary epilepsy in this population of dogs.

Materials and Methods

Criteria for case selection—Electronic and hardcopy records of a private referral hospital\(^9\) were searched to identify the records of dogs evaluated because of seizures (either local or generalized) between January 1, 2006, and December 31, 2011. All dogs included in the study were required to have a complete neurologic examination by a board-certified neurologist and an MRI analyzed by the neurologist or a board-certified radiologist. Only patients with a diagnosis of primary or secondary epilepsy were included in the study. Dogs were excluded if the age at seizure onset as reported by the owner was < 5 years or if they were known or suspected to have primary epilepsy. Results indicated that lack of abnormalities on neurologic examination does not exclude the possibility of intracranial lesions, and MRI with CSF analysis (when applicable) should be recommended for all dogs with onset of seizures at ≥ 5 years of age.
have reactive epilepsy resulting from toxin exposure, a metabolic syndrome, or an anesthesia-related incident.

Medical records review—Breed, sex, age at onset of seizures, results of neurologic examination, and diagnostic imaging results were obtained from the medical record. Results of hematologic, serum biochemical, and CSF analysis, other diagnostic tests performed, and diagnosis were recorded. Diagnosis of primary versus secondary epilepsy was made by the attending neurologist on the basis of analysis of the MRI and CSF findings.

Procedures—All dogs underwent screening tests, including a CBC, serum biochemical analysis, and thoracic radiography as part of the assessment for extracranial causes of seizures. When not contraindicated, a CSF sample was collected for analysis on-site and at a reference laboratory.

Additional testing for extracranial disorders included blood pressure measurement; assessment of circulating thyroid hormone (thyroxine and triiodothyronine), thyroid stimulating hormone, and bile acids concentrations; echocardiography; ECG; and abdominal ultrasonography. These evaluations were performed (in full or in part) when an extracranial cause of seizures was suspected. Other diagnostic tests were performed at the discretion of the attending neurologist and included measurement of serum antibodies against infectious organisms and PCR assays for evidence of rickettsial, protozoal, and fungal infections, or both types of testing.

All dogs underwent MRI of the brain. Dogs were anesthetized and placed in ventral recumbency, and scans were performed with a 0.2-Tesla MRI machine. Protocols included T1- and T2-weighted precontrast and spin echo imaging and T1-weighted postcontrast spin echo imaging in axial, coronal, and sagittal planes. At the discretion of the attending radiologist, FLAIR imaging was also conducted. Specific protocol information was not stated in the records. Dogs were presumed to have neoplasia when MRI images were consistent with mass lesions on the basis of accepted characteristics.15–17 The presence or absence of structural abnormalities on MRI was identified by the attending neurologist and radiologist.

Statistical analysis—Dogs were categorized by age at seizure onset with the following stratifications: 5 to 7, 8 to 10, 11 to 13, and ≥14 years. These stratifications were created for ease of analysis. Within each age range, dogs were further stratified by diagnosis (primary or secondary epilepsy). A χ² test was used to determine if the prevalence of primary versus secondary epilepsy differed significantly among the 4 age groups. For dogs with secondary epilepsy, diagnoses were classified as neoplasia or other. A Fisher exact test was used to determine if the proportions of dogs with a diagnosis of neoplasia versus a diagnosis of another disease was significantly different between dogs in the youngest age category and each of the older age categories. Additionally, a χ² test was used to determine if abnormal neurologic examination results were significantly associated with structural brain pathologic changes. Finally, the sensitivity, specificity, and positive and negative predictive values of abnormal neurologic examination findings to predict secondary epilepsy in dogs that developed seizures at ≥5 years of age were calculated. Statistical analyses were performed manually. Values of P ≤ 0.05 were considered significant.

Results—Ninety-nine dogs (49 spayed females, 39 neutered males, 2 sexually intact females, and 9 sexually intact males) met the criteria for the study. Mixed breeds (n = 13), Labrador Retrievers (8), and Boxers (7) were the most common, with 9 other breeds represented. Thirty dogs were between 5 and 7 years of age, 29 were 8 to 10 years of age, 33 were 11 to 13 years of age, and 7 were ≥14 years of age. Thirty-five of 99 (35%) dogs had seizures with no identified underlying cause, whereas the remaining 64 (65%) had a lesion identified on MRI or had abnormal findings on CSF analysis. Conditions identified in dogs with a diagnosis of secondary epilepsy included intracranial mass lesions suspected to be neoplasia, encephalitis or other inflammatory syndromes, hydrocephalus, infarction, and cysts.

Seven of 30 (23%) dogs between 5 and 7 years of age, 13 of 29 (45%) dogs between 8 and 10 years, 13 of 33 (39%) dogs between 11 and 13 years, and 2 of 7 dogs ≥14 years had primary (idiopathic) epilepsy. There was no significant (P = 0.33) difference in the prevalence of primary versus secondary epilepsy among the 4 age groups.

Twelve of 23 (52%) dogs of the 5- to 7-year-old age group with secondary epilepsy were identified as having neoplasia, and 11 (48%) had lesions categorized as other (which included inflammatory or vascular disease and congenital malformations). All (16/16) dogs of the 8- to 10-year-old age group, 16 of 20 (80%) dogs in the 11- to 13-year-old age group, and all (5/5) dogs in the ≥14-year age group had a diagnosis of neoplasia as the cause of the secondary epilepsy. A significant (P ≤ 0.05 for all comparisons) difference among age groups was found in etiology of secondary epilepsy, with the proportion of dogs 5 to 7 years of age that had neoplasia lower than that of dogs in all older age categories.

Because of postseizure activity or sedation in some dogs, a reliable neurologic examination could not be completed for every patient. However, 86 dogs had a full neurologic examination performed by a neurologist, with 53 and 33 dogs having abnormal and normal findings, respectively. Neurologic abnormalities reported included circling, changes in mentation, abnormal cranial nerve function, and loss or decrease in proprioception. Of the 53 dogs that had abnormal examination findings, 42 (79%) had a lesion detected by MRI (n = 40) or had abnormal findings on CSF analysis (8; some dogs had both CSF and MRI abnormalities). Fifteen of the 33 (45%) dogs with normal examination results had secondary epilepsy diagnosed on the basis of MRI or CSF analysis results. Abnormal neurologic examination findings had sensitivity of 74% and specificity of 62% to predict secondary epilepsy, with positive and negative predictive values of 79%, and 55%, respectively.

Discussion—The estimated prevalence of idiopathic epilepsy in dogs ranges from approximately 0.5% to 5.7%.14,18,19 This parallels information in reports indicating that epilepsy affects approximately 50 million people, or 0.8% to 1% of the population, and is the most common disorder of the human nervous system.20 In a long-term study of Labrador Retrievers, most affected dogs were diagnosed as having primary epilepsy between 1 and 5 years of age,18 and this age group represents most of the epileptic dogs managed by veterinarians.21,22 In the present study of dogs with an onset of seizures at ≥5 years of age, the proportion of patients with a diagnosis of primary epilepsy ranged from 7 of 30 (23%) to 13 of 29 (43%), depending on age group (5 to 7, 8 to 10, 11 to 13, or ≥14 years), and the prevalence of primary versus secondary epilepsy was not significantly differ-
ent among age groups. In a recent study\textsuperscript{12} of 63 dogs ranging from < 1 to 13 years of age, 25% had primary epilepsy and 61% had either secondary or cryptogenic epilepsy. In another recent study\textsuperscript{11} 45 of 214 (21%) dogs > 7 years of age had no underlying cause of seizures identified; only 14 of 108 (13%) dogs > 10 years of age had no detectable lesions. Interestingly, the results of our study do not differ much from the aforementioned study\textsuperscript{11} even though our patients were all ≥ 3 years of age. Thirty-five of 99 (39%) dogs in our study population had primary epilepsy.

Among 5- to 7-year-old dogs with secondary epilepsy in the present study, the prevalence of neoplasia was similar to the prevalence of all other causes combined (inflammatory, vascular, or congenital conditions). The prevalence of neoplasia in dogs ≥ 8 years of age that had secondary epilepsy ranged from 16 of 20 (80%) to 16 of 16 (100%), depending on age group.

Of 53 patients in this study that had abnormal neurologic examination results, 42 (79%) had an intracranial abnormality detected by MRI or had abnormal CSF analysis results. However, a substantial proportion of dogs without any deficits on examination (19/33 [49%]) had a diagnosis of secondary epilepsy. Authors of a previous study\textsuperscript{4} concluded that detection of neurologic deficits during examination was a sensitive means for identification of secondary epilepsy, with normal neurologic examination results indicating primary epilepsy. However, the age range of patients in that study\textsuperscript{4} was 2.5 to 8.6 years, with a mean of 5.3 years. Our results clearly differ, as neurologic examination had low sensitivity and specificity for detection of secondary epilepsy. The difference in age range between studies may explain the discordant results.

The sensitivity of neurologic examination abnormalities to predict secondary epilepsy was 74%, with a specificity of 62%. The low specificity may have been attributable to postictal effects, considering that many examinations were performed within a short time after seizure activity was observed. The sensitivity of 74% suggests that a considerable number of canine patients with normal neurologic examination results may be inappropriately presumed to have primary epilepsy if MRI and CSF analysis are not performed. With a negative predictive value of only 53%, a negative result (ie, normal findings on neurologic examination) would not exclude the possibility of an intracranial lesion. Therefore, our results indicate that MRI and CSF analysis when applicable, should be recommended to owners of all dogs ≥ 5 years of age with new onset of seizures, regardless of neurologic examination results.

Currently in veterinary medicine, it is often presumed that any dog with late onset of seizures (≥ 5 years of age) is unlikely to have primary epilepsy;\textsuperscript{22,23} and many practitioners associate the age of seizure onset with underlying cause.\textsuperscript{10} Given that complete neurologic assessments are expensive,\textsuperscript{21} many owners may elect to forego advanced diagnostic testing because of a high likelihood of intracranial pathological changes, particularly for the reason that treatment options for dogs with many of these diseases are costly and invasive.\textsuperscript{22,23} Although most patients in the present study had secondary epilepsy, a considerable percentage (7 of 30 [23%] to 13 of 29 [44%, depending on age group) of older dogs with new-onset seizures had a diagnosis of primary epilepsy and thus a possibly better prognosis than might generally be expected.\textsuperscript{10}

One limitation of this study was its retrospective nature, which prevented the standardization of diagnostic assessments. In addition, dogs were classified with neoplasia solely on the basis of MRI findings. Definitive diagnosis would have required brain tissue biopsy, which was not performed. Another limitation was the possibility of misclassifying dogs as having primary epilepsy because of the limitations of the MRI unit used.\textsuperscript{26} An MRI unit with a larger magnet or additional spins may have reduced this limitation. The rate of MRI detection for structural lesions associated with epilepsy in animals is much lower than in humans.\textsuperscript{8} Even though MRI is approximately 90% sensitive for detection of neoplasia, a study\textsuperscript{25} of people showed only 38.9% sensitivity for detection of cerebrovascular disease. Some dogs with secondary epilepsy in our study may have been classified inappropriately as having neoplasia versus another structural abnormality.\textsuperscript{25} Even in human patients, not all structural lesions can be diagnosed with MRI.\textsuperscript{8} However, MRI is accepted as the best way to evaluate the nervous system, compared with other imaging modalities. In addition, MRI is the most sensitive and specific test for differentiation of various neurologic structural diseases.\textsuperscript{25}

Additionally, in the circumstance of an early-onset lesion, some of the dogs of the present study may have gone on to develop a detectable structural lesion over time. Long-term follow-up of the patients, especially those with a diagnosis of idiopathic epilepsy, would have helped decrease this limitation. Despite these limitations, results of our study suggest that a considerable portion of older dogs that develop epilepsy have no evidence of structural disease at the time of diagnosis.

The application of sensitivity and specificity of abnormal neurologic examination findings to detect intracranial abnormalities in a general population of dogs should be cautioned against. Although examinations are dependent on the practitioner and patient status, other studies\textsuperscript{8,24} have shown that deficits in neurologic examinations are sensitive for detection of secondary epilepsy. However, almost half of the dogs with secondary epilepsy in our study did not have detectable neurologic deficits.

Although care was taken to include only those dogs that were not in a postictal state and were not receiving any anticonvulsant medication at the time of examination, these variables could not be fully controlled for. Such patients may have been mistakenly classified as having neurologic deficits. However, our data still suggest that advanced diagnostic testing should be recommended for evaluation of dogs with new onset of seizures ≥ 5 years of age, regardless of neurologic examination results. This is in agreement with recommendations made by the human International League Against Epilepsy, which include evaluation with MRI for every patient with seizures.\textsuperscript{8}

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References

From this month’s AJVR

Cardiovascular effects of dopamine hydrochloride and phenylephrine hydrochloride in healthy isoflurane-anesthetized New Zealand White rabbits (Oryctolagus cuniculus)

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Objective—To determine the cardiopulmonary effects of progressively increasing infusion rates of dopamine hydrochloride and phenylephrine hydrochloride in healthy adult New Zealand White rabbits (Oryctolagus cuniculus) anesthetized with isoflurane.

Animals—6 New Zealand White rabbits.

Procedures—Each rabbit was anesthetized on 2 occasions (≥ 2 weeks apart) with isoflurane in oxygen at 1.5 times the published isoflurane minimum alveolar concentration of 2.07%. Carotid artery and pulmonary artery catheters were placed. During each anesthetic episode, each rabbit received 5 progressively increasing doses of either dopamine (5, 10, 15, 20, or 30 µg/kg/min) or phenylephrine (0.125, 0.25, 0.5, 1.0, and 2.0 µg/kg/min). Blood gas and cardiopulmonary measurements were obtained after a 20-minute equilibration period prior to administration of the first drug dose (baseline) and after each subsequent dose administration.

Results—Dopamine increased stroke index at the highest infusion rate of 30 µg/kg/min; however, cardiac output and mean arterial blood pressure remained unchanged from baseline values. Administration of phenylephrine at a rate of 2 µg/kg/min increased mean arterial blood pressure to 62 mm Hg from the baseline value of 45 mm Hg. This was a result of an increase in systemic vascular resistance with a concomitant decrease in heart rate and no change in cardiac output. Blood lactate concentration increased with time when rabbits received either treatment.

Conclusions and Clinical Relevance—Within the dose range of 5 to 30 µg/kg/min, dopamine was not an effective treatment for isoflurane-induced hypotension in rabbits and phenylephrine was only minimally effective at a dose of 2 µg/kg/min. [Am J Vet Res 2015;76:116–121]